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ENSURING SAFE MEDICINES AND MEDICAL DEVICES FOR CHILDREN

HEARING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED TENTH CONGRESS

FIRST SESSION

ON

EXAMINING ENSURING SAFE MEDICINES AND MEDICAL DEVICES FOR CHILDREN

MARCH 27, 2007

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ENSURING SAFE MEDICINES AND MEDICAL DEVICES FOR CHILDREN

TUESDAY, MARCH 27, 2007

U.S. SENATE,
COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS,
Washington, DC.

The committee met, pursuant to notice, at 1:09 p.m. in room SD–430, Dirksen Senate Office Building, Hon. Christopher J. Dodd, presiding.

Present: Senators Dodd, Clinton, Brown, Alexander, and Allard.

OPENING STATEMENT OF SENATOR DODD

Senator DODD. The committee will come to order and I want to welcome my colleague and good friend, Lamar Alexander, who chaired this committee for some time. I've enjoyed his friendship and also working with him immensely during our time here together in the U.S. Senate. I thank you for being with us this morning. I want to thank our witnesses as well, for their participation, some of whom I've dealt with a lot over the years on a variety of issues affecting children and families and I want to thank Senator Kennedy for calling this important hearing on ensuring safe medicines and medical devices for children.

At today's hearing, we'll look at two programs that are due to be reauthorized this year, the Best Pharmaceuticals Act, BPCA and the Pediatric Research Equity Act, the PRE Act as well as—there are three of those—as well as an initiative I've introduced, the Pediatric Medical Device Safety and Improvement Act of 2007.

I want to take a minute here before we get into the substance of this and he's not here any longer. He doesn't sit at this dais any longer but of all the bills I did for so many years involving this issue and others, Mike DeWine of Ohio was a very valued partner on these issues and he was defeated last fall for re-election. But he did a wonderful, wonderful job, time and time again, on these questions and I just want the record to recognize that a lot of what we're talking about here doesn't happen miraculously, it happens because good people on the both sides of the political spectrum and isle care about these issues and Mike DeWine was one of those people and so I'd like the record to reflect my deep appreciation of Mike's work in this area over the years.

The story of the Better Pharmaceuticals Act for Children is one of huge successes for children and their families, children with a wide range of diseases such as HIV/AIDS, cancer, allergies, asthma, neurological and psychiatric disorders and obesity, can now

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lead healthier, more productive lives as a result of new information about the safety and efficacy of drugs they use to treat and manage their diseases, where previously there was none.

Pediatric drug studies conducted by the BPCA showed that children may have been exposed to ineffective drugs, ineffective dosing, overdosing or the side effects that were previously unknown. Since BPCA's passage in 1997 and its real authorization in 2000, the FDA has requested nearly 800 studies involving more than 45,000 children in clinical trials. Useful new pediatric information is now part of product labeling for 119 drugs as a result of those efforts.

By comparison, just to put it in perspective for you, in the 7 years prior to the adoption of BPCA, there were only 11 studies of marketed drugs that were completed in that timeframe. In the past 10 years, there has been a nearly 20-fold increase in the number of drugs studied in infants and children and adolescents since BPCA was enacted.

The labeling changes resulting from clinical studies under BPCA have informed physicians of the proper dosing and the examples of Viracept, a protease inhibiter used in combination therapy for the treatment of HIV and Neurontin, a pain relief medication used to treat children with chronic pain. For children with epilepsy, BPCA studies informed physicians that the drugs Keppra and Trileptal could be used safely and effectively at an even earlier age than previously known. BPCA studies of Imitrex showed no better results than placebo for the treatment of migraine headaches in adolescents. These studies also showed serious adverse events due to Imitrex in pediatric populations and therefore the drug is not recommended to migraines in anyone less than 18 years of age.

Recent studies of BPCA by the Government Accounting Office and by several authors at Duke University and in articles that appeared in the Journal of the American Medical Association have demonstrated that the program is a success and identified opportunities to strengthen the program. Authors of the recent JAMA article found that outside BPCA, FDA is limited in the number and scope of studies to which it can require pediatric data for existing products on the market.

Contrary to statements that have been made about the program, data from this article showed that only a minority of drugs studied under BPCA, about 20 percent, had more than $1 billion in annual sales. In fact, the median drug granted exclusivity was a small market drug with annual sales of $180 million and 30 percent of the drugs showed had sales of less than $200 million. This article went to say that a universal reduction in the length of pediatric exclusivity from 6 to 3 months would mean that products with small profit margins may not be submitted for pediatric testing.

I recently circulated legislation to reauthorize BPCA, which I believe is a balanced and workable proposal that addresses several of the recommendations made by the General Accounting Office and the JAMA article. The author is including a provision to address the minority of cases where pediatric exclusivity has far exceeded the carrot it was intended to provide for drug sponsors.

I want to thank the many individuals and organizations in the pediatrics community and the pharmaceutical industry that worked with this subcommittee and the committee in crafting this proposal

and support the provisions contained within. Specifically, I'd like to recognize the work of Mark Del Monte of the American Academy of Pediatrics and Elaine Vining and Jeanne Ireland with the Elizabeth Glaser Pediatric Aids Foundation for the countless hours that they have devoted in order to provide my office with ideas and technical assistance for the reauthorization of BPCA.

BPCA has had a long history of bipartisan support. I want that to be the future of this initiative as well. I've not formally introduced this proposal as a bill in the hopes that it will garner bipartisan support upon introduction. After all, the safety of our Nation's children is not a partisan issue—it should never be.

We'll also hear from expert medical device witnesses at today's hearing. The legislation I've introduced, the Pediatric Medical Device, Safety and Improvement Act provides a comprehensive approach to ensuring that children are not left behind as cutting edge research and revolutionary technologies for medical devices advance. Like drugs, where far too long children were treated like small adults, could just take reduced doses of adult products. Many essential medical devices used extensively by pediatricians are not designed or sized for children.

According to pediatricians, the development of new medical devices suitable for children's smaller and growing bodies can lag 5 or 10 years behind those for adults. The Pediatric Medical Device Safety and Improvement Act improves incentives for devices for small markets while still preserving the ability to ensure the safety of new products once on the market. It provides assistance to innovators, streamlines regulatory processes and elevates pediatric device issues at the FDA and NIH.

This legislation has been many years in the making and support for the legislation represents a broad range of interests, including the Medical Device Trade Association. Development of the bill involved the import and guidance of pediatricians, device manufacturers, both small and large ones, innovators and patient advocates.

We're going to hear testimony this afternoon shortly from Dr. Ed Rozynski from the Stryker Corporation, a medical device company that has been a long-standing and vigorous supporter of this initiative and I look forward to hearing your testimony.

As a parent of two young children, it is essential that products used in children's growing bodies, whether they be drugs or devices, are appropriately tested and designed specifically for their use. We must continue the tremendous success of BPCA and PREA by strengthening both programs through the reauthorization process this year. I'm a strong supporter of both programs and pleased to be an original co-sponsor of the reauthorization of PREA and my colleague from New York who has been the leader on this issue since her days at the White House and then here. I commend her immensely for her work so I'm going to turn in a minute for some opening comments, if I can, Senator and I thank you for your work in this area.

It is essential that we use these past experiences of both programs to ensure they continue to thrive in the future and that we have enough sense to look as to how they've developed over the last few years to make appropriate changes in the legislation so that we

reflect what has occurred and what we've learned over the past number of years as well. So with that, let me turn to my colleague from Tennessee and again, my thanks to Lamar Alexander for his wonderful leadership on so many of these issues during our tenure here together and I thank you immensely for that.

OPENING STATEMENT OF SENATOR ALEXANDER

Senator ALEXANDER. Thank you, Senator Dodd, Mr. Chairman and Senator Clinton. I enjoyed working with Chris Dodd on these issues and we've done that for the last 4 years and we'll continue to do more. I want to salute him for his leadership on helping to make sure that drugs that are prescribed for children are—that more is known about how safe they are when they are used and I want to salute Senator Clinton for her work on the Pediatric Research Equity Act. These two laws work together.

I don't have very much to say about either one of them. I'm looking forward to the testimony today and I look forward to working with Senator Dodd and Senator Clinton on making sure that we reauthorize the legislation. I don't think there is any disagreement, at least from my part, about whether we would reauthorize the legislation. The only questions that remain and that's why we have these hearings and discussions, is just how we should reauthorize them. What should we consider, what have we learned in the last few years and what should we do going forward?

Sometimes a statistic helps put things in—and relief in my State of Tennessee. In 1999, seven babies who were prescribed an antibiotic to treat whooping cough became so seriously ill that they needed stomach surgery. The Center for Disease Control linked their illness to the antibiotic, which had never been tested in young children. My information is that currently, only about one-third of drugs prescribed to children have been studied and labeled for children. That leaves too many physicians making guesses and it leaves too many worried parents.

So we believe we have some good legislation here. I should add that Senator DeWine did make a significant contribution to both pieces of legislation when he was here. I think he was the principle co-sponsor of both Senator Clinton's bill and Senator Dodd's bill and we salute him for that. So I look forward to working with my colleagues to reauthorize the legislation, to find the appropriate way to do it and I look forward to the hearing. Thank you, Senator.

Senator DODD. Thank you very much, Senator.

Senator Clinton.

STATEMENT OF SENATOR CLINTON

Senator CLINTON. Thank you so much and of course, Senator Dodd has such a long history of being on the forefront of all of the efforts we've made in the Congress over a number of years now, on behalf of children and families and it is a real pleasure to be here with both he and Senator Alexander. I'm pleased to be Senator Dodd's co-sponsor on the Pediatric Medical Devices Safety and Improvement Act when that is finally offered because it will improve the number and types of medical devices designed for pediatric populations and I particularly want to thank the witnesses today,

who are going to give the guidance that Senator Alexander said that we need to have and I welcome back Susan Belfiore and her family because she has been an advocate on behalf of these issues, along with her family, for a number of years now.

The type of drugs and the number of drugs that are available for children has been an issue for me for many years. Back during the Clinton Administration, I first worked with the Food and Drug Administration and the Elizabeth Glaser Pediatric AIDS Foundation and other patient groups to establish the Pediatric Rule, which requires that drug manufacturers ensure medications marketed for pediatric use are safe and effective for our children. Then when this regulation was challenged in court, I worked with my colleagues in the Senate, Senator Dodd and Senator DeWine, to get the Pediatric Rule enacted into law.

This landmark law, the Pediatric Research Equity Act was a real step forward. We can look at the changes and realize how much has occurred and yet still know we have a long way to go. As of the early 1990s, only about 20 percent of drugs contained specific pediatric dosing information but we know that children are not just little adults and a drug that reacts one way in an adult's body can have serious consequences in a child and as Senator Alexander said, we sometimes tragically discover this.

We've put pediatricians, in the past, into a guessing game, trying to determine if a drug appropriate for an adult would have the same pharmacological effect on a child. But thanks to the combined efforts, the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act, we're now able to use the best evidence to make better healthcare decisions for children.

We are now requiring submission of pediatric clinical trial data for new drug applications so that we can be better assured that drugs marketed for children are safe and effective. Indeed, more than 1,000 new and supplemental drug applications have fallen under the scope of the Pediatric Rule and the Pediatric Research Equity Act. The Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act have managed to increase our understanding of the way drugs work in a pediatric population.

For example, we've learned that a drug commonly prescribed for migraines in adults is not effective in pediatric populations and may actually cause serious adverse consequences. We've learned that methylphenidate, a drug prescribed for Attention Deficient Hyperactivity Disorder is processed more by adolescents than other age groups, therefore it requires different dosages. We've been able to collect data on drugs commonly used in children, like Azithromycin, an antibiotic used to treat bronchitis, pneumonia and respiratory infections as well as drugs that are not so commonly used but that help keep children alive, like Emtriva, one of the newer drugs we have to treat AIDS.

But both of these acts are scheduled to expire in September if they are not reauthorized. So that's why this hearing is so timely and important and I'll be introducing the Pediatric Research Improvement Act legislation that would reauthorize the Pediatric Research Equity Act and make permanent the FDA's authority to require submission of pediatric clinical trial data for drugs designed for children.

I just want to emphasize this one point. When both of these bills were passed, they had what are called sunsets, which means that you have to go back and reauthorize them. I think that there is general agreement that the Best Pharmaceuticals Act probably is one that a sunset is important for, to make sure that the incentives that Senator Dodd designed are working the way they should but it seems a little strange that we would have to reauthorize the Pediatric Rule. We don't have sunsets on getting adult clinical data to determine what happens with drugs in adults. We shouldn't have any kind of sunset on getting the same data for children. I think we should make this Pediatric Rule permanent and I will be introducing legislation to do that.

It will also improve the ability of the FDA to require testing on already marketed drugs when drug companies refuse to carry out that testing on their own and better coordinate the incentives in these important laws. So I'm very pleased to be here and to continue to work with my colleagues, led by Senator Dodd, to get this done.

Senator DODD. Thank you immensely for that and again, thanks for your terrific work on these issues over the years. It has been a pleasure to work with you and it is a good cause. It is making a difference every day.

We are delighted to have our witnesses with us. Let me briefly introduce them. Susan Belfiore, we welcome you back and your wonderful family. You and your husband, for those who are not familiar here, Susan Belfiore has five children and she is going to testify on behalf of the Elizabeth Glaser Pediatric AIDS Foundation and all of us up here have worked with the Foundation over the years on a number of different issues. She and her husband adopted four children from Romania, all of whom are HIV positive and Mrs. Belfiore will talk about the impact that the Pharmaceuticals for Children Act and the Pediatric Research Equity Act have had on her children and her family. It's wonderful to have you with us. You are so knowledgeable and we admire you immensely for the gift of life and what you've done for these delightful children you have.

Dr. Richard Gorman is a practicing pediatrician from Baltimore, Maryland and we thank you and I admire that gray hair you've got on your head, Doctor. It's forming a caucus here occasionally, of gray hairs.

[Laughter.]

Senator DODD. He is Chairman of the American Academy of Pediatrics section on Clinical Pharmacology and Therapeutics. Previously, Dr. Gorman ran a pediatric emergency department, an ambulatory center and was Medical Director of the Maryland Poison Center and we thank you immensely. I say this over and over again, over 26 years of working with these issues, but for the American Academy of Pediatrics, family medical leave never would have become the law of the land. The childcare legislation never would have happened. Infant screening, premature birth legislation that Senator Alexander and I have worked on together—it's just a remarkable group of physicians and I thank you every time you come before this committee, for the difference you've made as a

group of doctors who has just been really terrific over the years. We thank you for your work.

Dr. Samuel Maldonado is Vice President and Head of the Pediatric Drug Department Center of Excellence at Johnson & Johnson, pharmaceutical research and development. He joined J&J in February 2000 as Director of Pediatric Drug Development, received his degree from the National University of Honduras and his MPH from George Washington University and you've had a variety of other experiences over your career and we thank you immensely for your work and the contributions that J&J has made to our efforts here today. I also point out that he ran the FDA—joined the FDA rather, as a Medical Officer in the Division of Anti-Infected Drug Products and was subsequently in the Division of Anti-Viral Drug Products as well, so you have wonderful experience here.

Dr. Robert Campbell is a Professor of Orthopedics at the University of Texas, the Health Science Center at San Antonio and is a pediatric orthopedic surgeon, an inventor and a father of five children as well. He invented and developed and brought to market a life saving pediatric surgical device known as the vertical expandable prosthetic titanium rib. We call it VEPTR, which is what it is affectionately known as, which was approved as a humanitarian device exception in 2004 after 14 years of FDA trials. That is a new definition of tenacity, Doctor, for your work in that regard and we thank you today for being with us.

I've mentioned Ed Rozynski already, who is the Vice President of Global Government Affairs at Stryker Corporation. They are a leading medical technology company and have been a leader in products of significance for children over the years. Stryker has been an early and vigorous supporter of the legislative effort to ensure the safety of medical devices used in children and I thank them for their leadership in this effort. I would point out that Mr. Rozynski is a student of International Health and Care Systems for the past 20 years. Among his many accomplishments, working with past Administrations and the FDA to ensure that U.S. companies could export medical devices to other major industrialized countries where they have been approved but which have not been granted U.S. approval. So we thank you for your efforts on behalf of people around the world as well.

With that, let me begin with you Susan. I'm not going to be rigid about this but if you'd keep an eye on the clock, I want to just tell you any documentation—all of your statements, their full contents will be included in the record here today so if you can kind of get through this in 5 or 6 minutes so we can move along and then have a good question and answer period here on some of these issues, I'd appreciate it very much. Welcome to the committee.

STATEMENT OF SUSAN BELFIORE, ELIZABETH GLASER PEDIATRIC AIDS FOUNDATION, PRINCETON, NEW JERSEY

Ms. BELFIORE. Mr. Chairman and distinguished committee members, thank you so much for having me and my family here today. I am Susan Belfiore, mother of five children, four whom are HIV positive.

I want to thank Senator Dodd, Senator Clinton, Senator Alexander, Senator Kennedy, and Senator Enzi for your leadership on

this issue. My family and I participated in a conference 5 years ago to speak about the new Pediatric Rule legislation. I am honored to be back again today to let you know the difference that it has made in our lives and how important it is that medications continue to be tested specifically for use in children.

This issue is not settled by any means but the progress we have made is because of you. Thank you. You are all true champions for children. I would also like to thank the Elizabeth Glaser Pediatric AIDS Foundation for everything they do for children and families. Our children are living healthier lives because of their work.

I would like to take a moment to acknowledge my family behind me—my husband Bill and the five reasons why we're here today: our children. Ramona, Ionel, Loredana, Mihaela, and Aiden.

Senator DODD. Why don't you stand up to be recognized?

[Applause.]

Ms. BELFIORE. We are here today because our family, like so many other families throughout the country are dependent on the latest medications to keep our children healthy. As you heard, four of our five children have the AIDS virus. Mihaela and Loredana are taking life-sustaining medications.

Clearly, this is an issue that is close to my heart. As a parent, there is nothing more difficult than knowing your child is sick. You can often feel scared and frightened. But our family believes in miracles. But miracles won't happen without the correct medication and the correct dosing. Both of these can be achieved only through pediatric testing.

I still remember the first time when our then 8-year-old Mihaela was put on a cocktail of drugs that many AIDS patients—adult AIDS patients—were using. We took the medications out of the pillboxes and put them into a container that was decorated with horses. Mihaela loves horses. We had a silly hat party at the dining room table. We wanted to focus on what was positive instead of the fact that for a very long time and maybe for the rest of her life, Mihaela might be dependent on the these medications to keep her healthy.

But the truth is, Mihaela and Loredana and thousands of children like them are dependent on the latest medications to keep them healthy, strong and alive. That is why the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act are so important. Unless these laws are continued, many kids won't have a chance. They cannot afford to rely on guesswork. We've tried that and I can tell you personally, it does not work.

This binder here is the record of my children's medical life. For the past 14 years, I have cataloged all aspects of their health, charting their blood work every 3 months, what medications they are taking, what reactions they might be having to the medications.

Ten years ago, we thought Mihaela was taking an effective drug regimen for HIV. She was not. It turns out she had been undermedicated because the drug she was taking had not been sufficiently tested for use in children. Mihaela's health suffered. Her virus increased and once again, she started to pick up opportunistic infections. Mihaela had only used this medication for a few years before forming a resistance.

As a mother, I can tell you resistance is a scary word because it means your child has lost access to one more drug in a regime and a very limited supply of options. When the options run out, children suffer. I recently looked at a picture of the press conference from 5 years ago. I believe Senator Dodd's office has shared a copy of the picture with you—I was shocked when I saw Mihaela. She was underweight and she looked sick. When you're in the moment, you don't realize it, until you go back. I could see how poorly she was doing.

In the last 5 years though, things have been really different. I have to say that again. For the last 5 years, things have been really different. For the first time, Mihaela is taking medication that was tested specifically for use in children. The results have been dramatic. Mihaela has grown, she has put on weight, her energy is incredible and she is free of infections. And the best part of it is that for the last 4 years, she has had undetectable virus in her system. She now loves and rides horses more than ever before.

My family's personal struggle is with HIV. But I have to point out that the value of these laws goes beyond HIV and beyond my individual family. My family and I are here for parents and children—all parents and all children, not just those living with AIDS. We have heard the statistics—about three-quarters of prescription medications have not been tested for use in children. These drugs are for everything from cancer, asthma, HIV and AIDS.

Now I understand that testing drugs for use in children is an additional expense for the drug companies. I also understand that it can be difficult to conduct studies because of a variety of enrollment issues. That is why BPCA includes an incentive for companies to do pediatric studies. That law is working well and it should be continued and I know others on this panel will speak to you more about that.

But this issue is just not about profit and the bottom line. It must be about the value of a child's life. To be honest, I wonder why testing medication in children is even a question. As adults, we wouldn't take medications that have not been tested for us, so why then, would we give them to our children?

That is why I strongly believe that the Pediatric Research Equity Act should be made permanent. My children come from a country that didn't have the resources to invest in its children, all its children, especially sick ones. Those were horrific times for Romania and they did the best they could. But I am here to say that we can do better. In the end, it's all about the children.

When it comes to medication, we know children are not just small adults. We know these laws work. We know there are still so many drugs out there that have not been tested for children and we know that now that we have this awareness, there can be no going back.

I appeal to you on behalf of my children and millions of children that are just as precious and important as they are, to reauthorize these laws as soon as possible. Surely we can agree that children deserve nothing less than the same information about safety and dosing of drugs that we demand for ourselves as adults.

Thank you again for inviting me here today on behalf of all parents. Thank you so much for all you do for children.

[The prepared statement of Ms. Belfiore follows:]

PREPARED STATEMENT OF SUSAN BELFIORE

Mr. Chairman and distinguished committee members. Thank you so much for having me and my family here today. I am Susan Belfiore, mother of 5 children, 4 of whom are HIV-positive.

I want to thank Senator Dodd, Senator Kennedy, Senator Enzi, Senator Alexander, and Senator Clinton for your leadership on this issue. My family and I participated in a press conference 5 years to announce the new Pediatric Rule legislation. I'm honored to be back again today to let you know the difference it has made in our lives and why it's so important that medications continue to be specifically tested for use in children.

This issue is not settled, by any means, but the progress we have made is because of you. You are all true champions for children. And I wanted to thank you.

I'd also like to thank the Elizabeth Glaser Pediatric AIDS Foundation for everything they do for children and families. Our children are living healthier lives because of their work.

I'd like to take just a moment to acknowledge my family behind me—my husband Bill, and the five reasons why I am here: my children, Ramona, Ionel, Loredana, Mihaela, and Aiden. We are here today because our family—like so may other families throughout the country—is dependent on medications to keep our children healthy. As you just heard, four of our five children are living with the AIDS virus. Mihaela and Loredana are taking life-sustaining medications.

So clearly, this is an issue that I hold close to my heart. As a parent, there is nothing more difficult than knowing your child is sick. You feel scared. Frustrated. Terrified. Helpless. You put your trust in doctors, and researchers, and the latest medications—and then you force yourself to believe.

Our family believes in miracles. But miracles won't happen without the correct medication and their correct dosing. Both of these can be achieved only through pediatric testing.

I still remember the first time we put our then 8-year-old daughter Mihaela on the cocktail of drugs used by many AIDS patients. We took the medications out of the pill boxes and put them into a container decorated with horses. Mihaela loves horses. We had a silly hat party at the dining room table. We wanted to turn the whole event into something that was positive, instead of focusing on the fact that for the rest of her life, Mihaela would be dependent on the latest medications to keep her alive.

But the truth is that Mihaela and Loredana and thousands of children like them ARE dependent on the latest medication to keep them healthy and strong and alive. And that is why the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act are so important.

Unless these laws are continued, these kids won't have a chance. They cannot afford to rely on guesswork. We've tried that, and I can tell you personally that it just doesn't work.

This binder is the story of my children's medical life. In it I have cataloged all the details of their illnesses—everything, including drug regimens, drug reactions, blood work, and hospitalizations. It's a visible reminder, to me, of the control and responsibility I have against a disease where so much is unknown.

Seven years ago, we thought Mihaela was taking an effective drug regime for HIV. She was not. It turns out she had been undermedicated because the drug she was taking had not been studied sufficiently for use in children. Mihaela's health suffered. Her virus increased. Once again, she started to pick up opportunistic infections.

Mihaela had only used this medication for a few years before forming a resistance. As a mother, resistance is a very scary word because it means your child has lost access to one more drug regime, one in a very limited supply of options.

And when the options run out, children suffer and even die.

Recently I looked at a picture of that press conference from 5 years ago. I was shocked when I saw Mihaela. She was underweight. She looked sick. When you're in the moment, you don't realize it, until you go back. In this photo, you can really see just how poorly she was doing.

In the last 6 years, though, things have been different. For the first time, Mihaela has taken medication that WAS tested specifically for use in children. The results have been dramatic. Mihaela has grown, put on weight, and has been free of infections. And for the last 4 years she has had undetectable virus. Her love of horses has grown too.

Thank you.

My family's personal struggle is with HIV. But I have to point out that the value of these laws goes beyond HIV, beyond my individual family. I, and my family, are here for all parents, and especially for all children, not just those living with HIV and AIDS. We've all heard the statistic: About three-quarters of prescription medications have not been tested for use in children. These are drugs for everything from asthma and allergies, to high blood pressure and HIV/AIDS.

As parents, we need to know that we are doing the very best that we can for our children. We never give up. We never say no to what our children need, especially when it comes to medicines that can save their lives. And I can't imagine our government leaders would either.

Now, I understand that testing drugs for use in children is an additional expense for drug companies. And I also understand that it can be difficult to conduct the studies because of a variety of enrollment issues. That's why BPCA includes an incentive for companies to do pediatric studies. That law is working well and should be continued. And I know others on this panel will talk to you more about that.

But this issue cannot just be about profits and the bottom line. It must be about the value of a child's life. To be honest, I wonder why the idea that all medications should be studied for children is even a question. As adults, we wouldn't take medications that were not tested for us. So why would we give them to our children?

And that is why I strongly believe that the Pediatric Research Equity Act should be made permanent.

My children come from a country that didn't have the resources to invest in all its children—especially sick ones. Those were horrific times for Romania and they did the best they could. But I'm here to say that we can do better. I'm here today to tell you that my children, and millions of children like them, are worth investing in. It sounds like such a strange thing to say. How can there even be a question?

And this investment doesn't just apply to drugs. Senator Dodd has introduced legislation that applies the lessons we have learned about safe drugs for children to the world of medical devices. Children often rely on medical devices, such as heart pumps and ear implants, to treat serious conditions and illnesses. Yet there are so few medical devices designed specifically for children. So doctors must improvise, and sometimes, children are hurt in the process. Let us not repeat past mistakes and leave children behind as science and technology move forward.

In the end, this is all about children. These laws are basic investments in our children's future. We know they work and we know they are saving lives.

I appeal to you on behalf of Ramona, Ionel, Loredana, Mihaela, Aiden, and millions of other children just as precious and important as they are, to reauthorize these laws as soon as possible. Surely we can agree that our children deserve nothing less than the same information about the safety and dosing of drugs that we demand for ourselves as adults.

Thank you again for inviting me here today. And on behalf of all parents, thank you so much for all you do for our children. I can tell you personally, you are making a real difference.

Senator DODD. Thank you very, very much, Ms. Belfiore. We appreciate it very much and thank you for bringing your family along. It's wonderful to have you here with us today and seeing you all doing so very, very well. I remember very well the gathering about 5 years ago when we saw all of you. It's nice to have you back with us. Thank you for coming. Thank you for your testimony and your work as well.

Dr. Gorman, thank you for joining us.

STATEMENT OF RICHARD GORMAN, M.D., FAAP, PEDIATRICIAN AND CHAIR OF THE AMERICAN ACADEMY OF PEDIATRICS' SECTION ON CLINICAL PHARMACOLOGY AND THERAPEUTICS, BALTIMORE, MARYLAND

Dr. GORMAN. Mr. Chairman and members of the committee, I am Richard Gorman, a practicing pediatrician who has taken care of infants, children and adolescents for over 25 years. I thank the committee for holding this hearing on the need for safe and effective drugs and medical devices for children and after reading Susan's testimony last night, I took out the same set of pictures and

I remembered that press conference and Senator DeWine and Senator Frist and Senator Clinton and yourself standing there in the front of the room, realizing that something good had happened for children that day. I wanted to bring that back up because it was a wonderful time for us as well.

Senator DODD. Thank you.

Dr. GORMAN. If I learned anything at the last conference, it's that you should never have to speak after Susan.

[Laughter.]

Dr. GORMAN. Which was exactly my placement the last time as well. This is another learning experience for me. In my practice at Pediatric Partners in Maryland, I see first-hand the pediatric therapeutic benefits of increased pediatric information. With over 80,000 pediatric visits annually to our practice sites, my partners and I can attest to the importance of pediatric drug studies.

I am here today on behalf of the American Academy of Pediatrics to discuss the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, which are critical public policy successes for children. I wish to extend the Academy's sincerest thanks to both Senators Dodd and Clinton for their long support for championing these important bills.

I can say without reservation that in the last decade, we have gained more useful pediatric drug information through these two laws than we had in the previous 70 years. It is vitally important for children that these laws be reauthorized. The Academy is pleased to support the draft BPCA reauthorization proposed for release by Senator Dodd and the PREA reauthorization legislation soon to be introduced by Senator Clinton.

In previous testimony before Congress, I have described children as the canaries in the mine shafts. They have always acted as the early warnings of unknown dangers in therapeutics. BPCA and PREA work together to help protect our children from these dangers. These two pieces of legislation create an effective two-pronged approach to generate knowledge about the drugs we use in children.

However, despite the important advances resulting from BPCA and PREA, there is still much more to learn. Still today, nearly two-thirds of drugs used in children are not labeled for them. When children are in hospitals, 80 percent of them receive at least one drug that is for an off-labeled use, much like the Arthrithomycin used in the State of Tennessee, for these children with pertussis that were a little young to get that medicine. Therefore for children, off-label use remains the rule and not the exception.

Mr. Chairman, in my written testimony, I have elaborated on the recommendations for improvements for these legislations in several areas. We believe that Senators Dodd and Clinton have addressed AAP's concerns well in their respective reauthorization bills. Both proposals work together to maximize the historic opportunity to pass a well-coordinated and effective packet of legislation that will benefit all children.

The proposed legislation increases the dissemination, the transparency and the tracking of pediatric drug information. It streamlines and integrates the FDA Administration of BPCA and PREA to improve the uniformity, the consistency and the quality of pedi-

atric studies and it expands the study of off-patented or generic drugs and addresses gaps in the understanding of pediatric therapeutics.

In addition, Senator Dodd's proposal for adjusting the exclusivity extension is a balanced compromise that will preserve the quality and the number of pediatric studies gained through BPCA.

It also addresses the concerns regarding excessive profits. We know that 6 months of additional marketing exclusivity has been very successful in the past in creating pediatric studies.

The AAP pledged to review any proposal for limiting the exclusivity awarded under BPCA using two criteria. First, any change must not reduce the number of drugs studied in children. The GAP found that drug sponsors agreed to conduct studies and proposals to written requests from the FDA 81 percent of the time. Any proposal that will decrease the number of favorable responses to a written request would undermine the essential goal of BPCA.

We have data published in the medical journals to show that simply cutting the incentive from 6 months to some lesser number will certainly reduce pediatric studies and we cannot support those proposals.

The second criteria we were using was administrative simplicity. Proposals using complicated formulas are likely to bog down the FDA and give rise to endless disputes between sponsors and the agency, including litigation. We cannot risk deterring or delaying important information getting into the hands of families and their healthcare providers.

The changes proposed by Senator Dodd are straightforward and as clear as possible. It targets only those blockbuster drugs for which an appropriate reduction in exclusivity will not reduce acceptance of, and successful completion of, written requests for blockbuster drugs.

We also support Senator Clinton's legislation that makes PREA a permanent part of the Food and Drug Act. The FDA currently has permanent authority to ensure the safety of drugs in adults. Children deserve the same. When PREA is reauthorized, it should be made permanent. Congress should not need to debate every few years whether or not they should continue to require safety testing for drugs for children.

It is useful, however, to re-evaluate the exclusivity program periodically to ensure that incentive offered achieved its desired goals, despite the dynamic pharmaceuticals market. Congress should have the opportunity every 5 years to analyze whether BPCA continues to strike the right balance between achieving critical pediatric information and providing an appropriate incentive to maintain the number and quality of pediatric studies.

In closing, I would like to thank the committee again. I would like to reiterate the strong support of the American Academy of Pediatrics for reauthorization of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. We urge their renewal as part of the package of FDA bills under consideration by this committee for the sake of all the children in the United States. I'll be happy to answer any questions later.

[The prepared statement of Dr. Gorman follows:]

PREPARED STATEMENT OF RICHARD L. GORMAN, M.D., FAAP

Mr. Chairman, members of the committee, I am Richard Gorman, M.D., FAAP, a practicing pediatrician who has taken care of infants, children and adolescents for over 29 years. I am here today representing the American Academy of Pediatrics (AAP) in my official capacity as chair of the AAP Section on Clinical Pharmacology and Therapeutics. It is through my practice, Pediatric Partners in Ellicott City, Maryland where I see firsthand the pediatric therapeutic benefits of increased information on drugs used in children. With over 80,000 pediatric visits annually in four clinical sites in three counties in Maryland, my partners and I can attest to the importance of pediatric drug studies legislation.

The pediatric academic research community that includes the Ambulatory Pediatric Association, American Pediatric Society, Association of Medical School Pediatric Department Chairs, and the Society for Pediatric Research also supports and endorses the Academy's testimony. These societies comprise academic generalist pediatricians, pediatric researchers, and full-time academic and clinical faculty responsible for the delivery of health care services to children, the education and training of pediatricians, and the leadership of medical school pediatric departments.

THE SUCCESS OF BPCA AND PREA

I am here today on behalf of the American Academy of Pediatrics to discuss the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), which represent critical public policy successes for children. I begin my testimony today by saying enthusiastically and without reservation that in the last decade we have gained more useful information on drugs used in children through BPCA and PREA than we had in the previous 70 years.

I wish to extend the Academy's sincerest thanks to Senators Dodd and Clinton for their long support and for championing these important bills. These two pieces of legislation have advanced medical therapies for infants, children, and adolescents by generating substantial new information on the safety and efficacy of pediatric pharmaceuticals where previously there was none. It is vitally important for infants, children and adolescents that these laws be reauthorized.

In previous testimony before Congress, I have described children as "the canaries in the mineshafts," acting as early warning of unknown dangers. Legislative progress on drug safety for all Americans has most often been made after the tragic injuries or deaths of children. Despite this history, little progress was made in the effort to include the pediatric population in therapeutic advances until passage of the pediatric studies provision of the Food and Drug Administration Modernization Act of 1997 (FDAMA). This provision was later reauthorized as BPCA in 2002, and PREA was enacted in 2003. With the passage of this legislation, we have started to remedy the alarming lack of pediatric drug labeling and information available to pediatricians and other health professionals.

BPCA and PREA work together as an effective two-pronged approach to generate pediatric studies. PREA provides FDA the authority to require pediatric studies of drugs when their use for children would be the same as in adults. BPCA provides a voluntary incentive to drug manufacturers of an additional 6 months of marketing exclusivity for conducting pediatric studies of drugs that the FDA determines may be useful to children.

Since the passage of FDAMA over a decade ago, FDA has requested nearly 800 studies involving more than 45,000 children in clinical trials through a written request. The information gained from these studies resulted in label changes for 119 drugs.[1] By comparison, in the 7 years prior to FDAMA, only 11 studies of marketed drugs were completed, though 70 studies were promised. Similar data tracking PREA's effectiveness is not publicly available. AAP hopes this year's reauthorization will create that tracking system.

As a clinician, I cannot overstate the importance of what we have learned through the pediatric studies generated by these laws. Children's differing metabolism, growth and development, and size have very large effects. The performance of medications in children's bodies is even more dynamic and variable than we anticipated. Indeed, we have really learned, once again, that children are not just small adults. And the more we learn, the more we realize we didn't know.

For example, pediatric studies and resultant labeling have:

• given pediatricians the ability to give the correct dose of pain relief medicine to children with chronic pain that were previously under dosed (Neurontin®);

[1] American Academy of Pediatrics. Pediatric studies lead to more information on drug labels. *AAP News.* 2007;2:20–25.

• warned ICU physicians that a drug used for sedation in ICUs had twice the mortality rate as another drug combination (Propofol®)≧

• given pediatricians and child psychiatrists important information on both the relative effectiveness and serious side effects of anti-depressant medication in adolescents (Prozac®, Παχιλ®, ετ αλ.)≧

• given children increased relief of pain from medicines taken by mouth, breathed into the lungs, given through the vein, and absorbed through the skin; and,

• alerted both pediatricians and parents about unexpected side effects of medications that have allowed for a more complete discussion of both the risks and benefits of a particular therapeutic course.

What a tremendous improvement over the shrugging shoulders and the resigned look and the soft sigh when we had to say: "I'm sorry, we just don't know enough about this drug in children."

If a drug is not labeled for children, pediatricians are faced with two difficult choices: (1) not using a medication that could provide relief and help to the child because it is not labeled for use in pediatrics or (2) using the medication off-label based on limited studies and/or the clinical experience of health professionals. BPCA and PREA have given pediatricians more information to avoid this necessary but inadequate practice.

Better labeling has lead to better therapeutics for children, reducing medical errors and adverse effects. Lack of proper information for pediatric patients related to dosing, toxicity, adverse effects, drug interactions, etc. can lead to medical errors and potential injury. Medication errors produce a variety of problems, ranging from minor discomfort to substantial morbidity that may prolong hospitalization or lead to death. Another important factor underscoring the need for better labeling is the increasing effort of private and public payors to limit reimbursement for drugs prescribed off-label.

Increased pediatric studies also encourage the creation of child-friendly drug formulations. Even the most effective drug cannot improve a child's health if the drug is unavailable in a formulation that a child can take (e.g., pills vs. liquid) or if the taste is unpalatable. Compliance with a prescription often relies on the formulation. If a parent has to struggle with the child every time a dose is needed, the likelihood of completing the full prescription to obtain maximum benefit is greatly reduced. Again, here BPCA and PREA have been successful in informing what pediatric formulations are effective for children.

BPCA AND PREA ARE STILL ESSENTIAL TOOLS

Despite the advances resulting from BPCA and PREA, there remains much progress to be made. Children remain second-class citizens when it comes to drug safety and efficacy information. Currently, nearly two-thirds of drugs used in children are still not labeled for children.[2] Almost 80 percent of hospitalized children receive at least one drug prescribed to them for an off-label use.[3] For children, off-label use is the rule, not the exception, because of the scarcity of prescribing information for this population. Therefore, both BPCA and PREA are still crucially important and must be reauthorized this year, including needed improvements.

This year is the first time BPCA and PREA will be reauthorized together, providing Congress with an historic opportunity to pass a well-coordinated and effective package of legislation for the benefit of all children. We recommend the following improvements.

Increase the dissemination, transparency, and tracking of pediatric drug information. Dissemination of pediatric information to families and healthcare providers should be increased in both BPCA and PREA. If families choose to involve their children in a clinical trial for a drug, then the drug label should reflect that study. The Government Accountability Office (GAO) found that about 87 percent of drugs granted exclusivity under BPCA had important label changes.[4] This is good news but it is our view that every drug label should reflect when a pediatric study was done (either through BPCA or PREA) and the results of the study, whether the results are positive, negative, or inconclusive. Moreover, FDA and drug sponsors must do more to communicate these label changes to pediatric clinicians. FDA should continue and expand its periodic monitoring of adverse events for both PREA and BPCA as this has been a useful tool to evaluate drug therapies after approval.

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[2] United States Government Accountability Office. Pediatric Drug Research. (GAO–07–557); 1.

[3] Shah SS, Sharma VS, Jenkins KJ, Levin JE. Off-label Drug Use in Hospitalized Children. *Arch Pediatr Adolesc Med.* 2007;161:282–290.

[4] GAO 2007; 16.

The transparency of the written request process used by FDA can be improved. Increased transparency will be beneficial to pediatricians, sponsors and families. AAP recommends that written requests be made public at the time FDA awards exclusivity and that each written request be allowed to include both off-label and on-label uses. Moreover, because we recognize that FDA has improved the pediatric study written requests since 1997, we recommend that the Institute of Medicine be engaged to review a representative sample of all written requests and pediatric assessments under PREA. This scientific review will provide recommendations to FDA to continue to improve the consistency and uniformity of pediatric studies across all review divisions within the FDA's Center for Drug Evaluation and Research.

Information regarding the number of written requests issued as well as information regarding pediatric studies and label changes made as a result of BPCA is tracked and posted at FDA's Web site. This information is key to understanding the operation of the law for children and we recommend that FDA also be required to track this information for PREA and make such information available.

Integrate and strengthen BPCA and PREA administrative processes. In general, BPCA and PREA processes are working well at FDA but more often as parallel programs than one administratively integrated pediatric study program. AAP supports the expansion of the existing internal FDA pediatric committee to include additional kinds of expertise within the agency and an integrated approach to the review and tracking of all pediatric studies requested or required by FDA, including the ability to require labeling changes.

Expand study of off-patent drugs. BPCA and PREA work well for new drugs and other on-patent drugs for which increased market exclusivity provides an appropriate incentive. However, for generic or off-patent drugs, BPCA and PREA have had a less effective reach. At the last BPCA reauthorization, Congress tasked the National Institute for Child Health and Human Development (NICHD) with creating a list of off-patent drugs needing further study in children and with conducting those needed studies. Although Congress never appropriated any funding to NICHD for this purpose, NICHD nevertheless has made significant progress identifying important off-patent drugs in need of study and starting clinical trials to study these drugs. AAP recommends that the role of NICHD be expanded in the current reauthorization to include study of the gaps in pediatric therapeutics in addition to generic or off-patent drugs. We also recommend PREA be strengthened so that needed pediatric studies can be conducted while drugs remain on patent.

BPCA also contains a mechanism through which pediatric studies of on-patent drugs declined by the sponsor can be referred to the Foundation for the National Institutes of Health (FNIH). FNIH is given authority to collect donations from pharmaceutical companies to fund such studies. Unfortunately these donations were not forthcoming, and, as reported in the GAO report, no studies have been completed using this mechanism. The Academy recommends retaining the legal authority of FNIH to maintain an emphasis on children and raise money from drug companies for important pediatric needs, such as training pediatric clinical investigators, building pediatric research networks and studying pediatric disease mechanisms. However, the mandate to conduct pediatric studies of on-patent drugs should not be continued.

Maintain quality and number of pediatric studies while addressing "windfalls." Providing drug companies 6 months of additional marketing exclusivity has been enormously successful in creating pediatric studies. The studies and label changes highlighted earlier in my testimony demonstrate this. Recent data shows that for the large majority of drugs, the return to companies for responding to a written request has not been excessive. The Journal of the American Medical Association published a study in February that showed the return to companies for performing pediatric studies varies widely.[5] Most companies who utilize BPCA made only a modest return on their investment in children.[6] However, for about 1 out of 5 companies with annual sales greater than $1 billion, the returns garnered through exclusivity have been very generous. Concerns regarding the returns to these "blockbuster" drugs have been voiced by several Members of Congress and a number of proposals have surfaced to limit or change the patent extension.

Any proposal to amend the pediatric exclusivity provision must not reduce quality and number of pediatric studies. The Academy has pledged to review any proposal for limiting the exclusivity awarded under BPCA using two criteria: first, any change must not reduce the number of drugs studied in children. GAO found that

[5] Li JS, Eisenstein EL, Grabowski HG, et al. Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program. *JAMA.* 2007;297:490–488.

[6] The median annual sales of a drug receiving pediatric exclusivity were $180 million with a return on investment of 1.5 times the cost of the study.

drug sponsors agreed to conduct studies in response to a written request from FDA 81 percent of the time.[7] Any proposal that will decrease the number of companies responding favorably to a written request from FDA would undermine the essential goal of BPCA. We now have data to show that simply cutting the incentive from 6 months to some lesser number across-the-board will certainly reduce pediatric studies and we cannot support such proposals.

The second criterion is administrative simplicity. Proposals for using complicated formulas are likely to bog down the administration of the program by FDA and give rise to endless disputes between sponsors and the agency—including litigation. We cannot risk deterring or delaying important information getting into the hands of families and their health care providers. Every additional variable that Congress gives FDA to evaluate, when considering awarding the incentive, adds an additional level of complexity and moves FDA further from its core regulatory expertise.

However, this does not mean that this issue should not be addressed. When this committee acts to reauthorize the exclusivity extension, we encourage you to make changes that are straightforward and as clear as possible, targeting only those "blockbuster" drugs for which an appropriate reduction in the exclusivity will not reduce acceptance and successful completion of written requests.

Make PREA a permanent part of the Food and Drug Act and continue to reevaluate BPCA. The FDA currently has the permanent authority to ensure the safety of drugs used in adults. Children deserve the same. When PREA is reauthorized, it should be made permanent. Congress need not debate every few years whether we should continue to require safety and efficacy information on drugs used in children. It is useful, however, to reevaluate the exclusivity program periodically to ensure that the incentive offered achieves its desired goal despite changes in the dynamic pharmaceuticals market. Congress should have the opportunity every 5 years to analyze whether BPCA continues to strike the right balance between achieving critical pediatric information and providing an appropriate incentive to maintain the number and quality of pediatric studies for on-patent medication.

CONCLUSION

I would like to thank the committee again for allowing me the opportunity to share with you the strong support of the American Academy of Pediatrics for reauthorization of BPCA and PREA. We urge their renewal as part of the package of FDA bills under consideration by this committee for the sake of all children throughout the United States.

I would be happy to answer any questions you may have.

Senator DODD. Thank you very much, Dr. Gorman. We're very grateful for your testimony. Dr. Maldonado, we appreciate your presence.

STATEMENT OF SAMUEL MALDONADO, M.D., MPH, FAAP, VICE PRESIDENT AND HEAD OF PEDIATRIC DRUG DEVELOPMENT CENTER OF EXCELLENCE, JOHNSON AND JOHNSON PHARMACEUTICAL RESEARCH AND DEVELOPMENT, RARITAN, NEW JERSEY

Dr. MALDONADO. Good afternoon, Mr. Chairman and members of the committee. My name is Samuel Maldonado. I am Vice President and Head of the Pediatric Drug Development Center at J&J and I appreciate the opportunity to testify today on these two programs.

I believe they have made a significant contribution to improving the availability and safety of medicines for children. Johnson & Johnson as a company and I personally applaud the leadership of this committee and especially Senator Dodd, in advancing issues related to children's health, the area to which I have dedicated my own life and career.

A pediatrician by training, I have spent almost a decade at the FDA as a Medical Officer where I participated in many aspects of

[7] GAO 2007; 12.

the regulatory process for development of pediatric medicines, including the Chair of the Working Group that helped develop the FDA's views on how medicines already approved for adults should be properly studied in children.

In almost two decades of work in pediatrics and drug development, I have seen many policies put forward with the aim of helping to ensure safe and effective medicines for children. None have had as profound and positive an impact as the Best Pharmaceuticals for Children Act, known as BPCA, together with the Pediatric Research Equity Act or PREA.

I urge you to renew these important pieces of legislation and grant them the permanence they merit by removing their sunset clauses. Together, BPCA and PREA working in synergy, provide both an incentive and a requirement crucial to the success of a robust program. PREA gives the FDA the authority to require pharmaceutical companies to conduct pediatric studies for certain uses in clinical development.

BPCA goes beyond PREA, encouraging manufacturers to ask, where are the unmet needs for children? And then pursue meaningful answers to that question under the guidance and direction of the FDA.

Since their enactment, BPCA and PREA have been catalysts for unprecedented advancements in pediatric drug research. The transformation that has been observed in pediatric drug development has been astounding, as the statistics outlined in my written testimony attest.

Prior to the flood of new data that BPCA and PREA have helped generate, pediatric pharmaceutical care was in many ways a guessing game. I saw this firsthand on an almost constant basis.

I just want to share with you one of the examples. Early in my career, when I was a Fellow at the FDA, I took an interest in metronidazole, a highly effective antibiotic used so widely that it was and still is administered even to premature babies. After reviewing the literature, I found no clinical data whatsoever, even in the dose that was recommended for children. There was only a paper written by Dr. John D. Nelson, an expert so well respected that he is considered the grandfather of pediatric infectious diseases. So I contacted him and asked him how he arrived at the dose? He said, "Son, I thought it was a good dose." This is, of course, no criticism of Dr. Nelson. He made his best judgments, as did we all, in the face of limited information. But when the health and well-being of children are at stake, we know that best judgments absent clinical data just aren't good enough. Children and all patients deserve better.

Under BPCA and PREA, pharmaceutical companies of all sizes, including J&J, are pursuing pediatric studies like never before and the benefits have been significant.

In recent years, pediatric information has been developed for a large number of medicines and formulations have been also developed for dose medicines. Formulations that remain available for children long after BPCA has expired—or the exclusivity has expired.

At Johnson and Johnson, we have conducted pediatric studies in areas ranging from autism to cancer to infectious diseases. We

have found that several medicines approved in adults were also effective in children, often at different doses but we have also found that some medicines used in adults do not work in children. These findings and continued studies have expanded our understanding of pediatric therapeutics and improve our development process for pediatric medicines.

To sustain the progress that BPCA and PREA have made possible and to strengthen the framework for future pediatric studies and infrastructure, the sunset clauses in both pieces of legislation should be permanently removed. By removing the sunset clauses, Congress will convey the powerful message that pediatric drug development is here to stay and drug safety and effectiveness for children is firmly among the Nation's highest priorities. The sunset clauses' removal will also help industry create and sustain the necessary infrastructure to continue improving pediatric therapeutics. All pediatricians know that more pediatric studies are needed. You can help them and the children they serve to get what they need.

In conclusion, the permanent renewal of BPCA and PREA is vital to continued progress in ensuring safe and effective medicines for children. No regulatory effort or legislation before these has come close to stimulating the kinds of advancements in pediatric drug safety and effectiveness that we've seen over the past decade.

Thank you again, Mr. Chairman and the committee, for your work on behalf of children's health and for giving me the opportunity to speak to you today. I look forward to answering any questions you may have.

[The prepared statement of Dr. Maldonado follows:]

PREPARED STATEMENT OF SAMUEL MALDONADO, M.D., MPH, FAAP

Good afternoon, Mr. Chairman and Members of the committee. My name is Dr. Samuel Maldonado, and I am Vice President and Head of the Pediatric Drug Development Center of Excellence at Johnson & Johnson Pharmaceutical Research and Development, speaking today on behalf of Johnson & Johnson, one of the world's largest providers of pediatric medicines. I am honored to come before you today as part of this important hearing to examine and affirm the best path forward to ensure safe and effective medicines for children.

Johnson & Johnson as a company and I personally applaud this committee for its leadership in advancing issues related to children's health. Indeed, it is the area to which I have dedicated my own life and career: After receiving my medical degree and completing my residency in pediatrics, I pursued a combined post-doctoral fellowship in pediatric infectious diseases and regulatory medicine at Children's National Medical Center, George Washington University, and the Food and Drug Administration (FDA) before serving at the FDA as a Medical Officer in the Center for Drug Evaluation and Research.

While at the FDA, I participated in several important aspects of the scientific and regulatory process relating to improving the development of pediatric medicines, including as Chair of the FDA Pediatric Pharmacokinetic Working Group that wrote the FDA Pediatric Pharmacokinetic Guidance for Industry, which set forth FDA's views on how medicines already approved for adults could be properly studied for children.

Today, my experience in pediatrics and in drug development spans almost two decades. In that time, I have seen many policies put forward with the aim of helping to ensure safe and effective medicines for children. None have had as profound and positive an impact as the pediatric provisions of the Food and Drug Administration Modernization Act of 1997 (FDAMA), appropriately renewed and expanded in 2002 as the Best Pharmaceuticals for Children Act (BPCA). This legislation provides for the possibility of 6 months of marketing exclusivity for a medicine in exchange for the voluntary completion of pediatric drug studies. As a result, it has spurred a tremendous increase in pediatric drug studies that is enhancing our knowledge of how

medicines work in children, in turn leading to the development of safer and more effective prescription medicines for children.

As we consider the topic today of ensuring safe medicines for children, I urge you to give priority attention to the need to renew the BPCA and its complementary legislation, the Pediatric Research Equity Act or PREA, this year. Moreover, I urge the committee to give these vital pieces of legislation the permanence they merit by removing the sunset clauses in both that are holding back, I believe, an even greater realization of their potential to stimulate further progress in pediatric drug research.

BPCA AND PREA: CATALYSTS FOR UNPARALLELED ADVANCEMENTS IN PEDIATRIC DRUG RESEARCH, SAFETY & EFFECTIVENESS

The reasons for reauthorization of BPCA and PREA are clear, numerous, and resounding. Together, they provide both an incentive and a requirement crucial to the success of a robust pediatric program. With that synergy in play, they have helped bring to light gaps in our understanding of pediatric pharmaceutical care and have created a highly successful incentives framework to foster the collection of targeted data to fill those gaps.

PREA gives the FDA the authority to require a pharmaceutical manufacturer to conduct pediatric studies for certain uses under clinical development. BPCA goes beyond PREA, encouraging manufacturers to ask, "Where are the unmet needs for children?"—including off-label uses—and then to pursue meaningful answers to that question under the guidance and direction of the FDA.

It is useful to remember that these laws were passed only after years of efforts by the FDA to encourage more pediatric studies and improved labeling for medicines that FDA knew were being used in the care of children. In 1994, FDA issued a regulation that it hoped would encourage sponsors to seek approval for pediatric uses. FDA also improved and streamlined the types of studies that could be used to bridge between adult and pediatric doses of medicines. That these efforts were not successful underscores the exceptional success of BPCA and PREA.

I have personally observed a night-and-day difference between pediatric drug development prior to the passage of BPCA and since. The transformation in this field has been nothing short of astounding, as the numbers alone attest: Since the pediatric study incentive program's original passage in 1997, there have been 492 pediatric proposals submitted to FDA. As of September of last year, the FDA had requested 782 pediatric studies. To date, the Agency has granted pediatric exclusivity for 132 approved products. More than 45,000 pediatric patients have participated in the studies over the last 10 years. Pharmaceutical companies of all sizes are pursuing pediatric studies like never before, for products at all levels of the sales volume spectrum.

The Center for the Study of Drug Development at Tufts University reported this month that the cumulative number of completed pediatric studies, subsequently accepted by the FDA, rose from 58 in 2000, when BPCA was first renewed, to 568 in 2006. In that same time period, the number of full safety and effectiveness pediatric drug studies conducted rose by a full 60 percent. This includes research into therapies for rare childhood diseases, including a significant number of pediatric cancer indications and treatments for serious illnesses such as pediatric AIDS, Crohn's Disease, bronchopulmonary dysplasia, and many others.

My personal experience as a pediatrician prior to BPCA and PREA—and the experiences of countless others in my field—substantiate the night-to-day transformation that has occurred with these important pieces of legislation. Prior to the flood of new data that BPCA and PREA have helped to generate, pediatric pharmaceutical care was in many ways a guessing game.

One experience from my early career aptly illustrates this predicament for pediatricians prior to the increase in pediatric clinical data: When I was carrying out my fellowship at the FDA, I took a keen interest in metronidazole, a widely used antibiotic in both adult and pediatric care administered even to premature babies but for which there appeared no clinical data to support the standard pediatric daily dosage of 30 milligrams for kilogram of body weight (mg/kg/day). After extensive review of the literature, I found only one reference to the 30 mg/kg/day dose for metronidazole, cited in a paper by Dr. John D. Nelson, the "grandfather of pediatric infectious diseases." A venerated expert, I contacted him to ask him how he arrived at the dose he recommended. He responded by saying, "Son, I just thought it was a good dose."

This is, of course, no criticism of Dr. Nelson. He made his best judgments—as did we all—in the face of very limited information. But when the health and well-being

of children are at stake, we know that best judgments absent clinical data just aren't good enough. Children—and all patients—deserve better.

At Johnson & Johnson, we have conducted pediatric studies in areas ranging from autism to cancer to infectious diseases. We have found that several medicines approved in adults were also effective in children, but often at different dose levels. Perhaps more importantly, we have found that some medicines used in adults do not, in fact, work in treating pediatric diseases. These findings and continued studies have steadily expanded our understanding of pediatric therapeutics, making possible important improvements to our development process for pediatric medicines.

How have all of these studies improved pediatric care in practice? To start, thanks to BPCA and PREA, we now have a wealth of new, more targeted, and complete information to help pediatricians and parents make the best possible treatment decisions for children in their care. This new information has helped us better understand the most appropriate drug dosing and access for pediatric patients, making treatment regimens safer and more effective.

According to a new study in the *Journal of the American Medical Association* (JAMA), prior to BPCA, about 70 percent of medicines used in children had been dispensed without adequate pediatric dosing information. In the 10 years since this legislation, close to 120 drug labels—or approximately 90 percent of the labels for products studied under BPCA and PREA—have been modified to reflect new pediatric-specific data. And as BPCA and PREA have made pediatric data collection and information dissemination common practice in the pharmaceutical industry, the time needed to make label changes to reflect this pediatric-specific data has fallen by 34 percent. This improved labeling includes, where necessary, information on products shown to be less effective or ineffective in pediatric patients. Switching pediatric patients off of less effective or ineffective medicines reduces unwarranted exposures, improving safety.

In addition, pediatric studies conducted since BPCA and PREA have resulted in the development of pediatric-specific formulations for a large number of medicines—formulations that have remained available long after pediatric exclusivity has expired.

Not surprisingly, the American Academy of Pediatrics (AAP) has hailed BPCA and PREA as "extraordinarily successful in generating important new information about the safety and efficacy of drugs used by children." Of course, even with all of this success, there is still much to learn in this area, hence the AAP's pronouncement that "we must not lose momentum in the quest for safer medications for children."

Johnson & Johnson echoes this sentiment. The area of pediatric drug development, as I've witnessed it, has burgeoned only in the last 10 years. There remains great need and potential for further discovery. To sustain the level of momentum that BPCA and PREA have spurred, and to strengthen the framework for further pediatric drug studies and infrastructure, we strongly believe that the sunset clauses in both pieces of legislation should be removed swiftly and permanently.

REMOVING THE SUNSET CLAUSES IN BPCA AND PREA: SOUND POLICY FOR ENSURING FURTHER ADVANCEMENTS IN PEDIATRIC DRUG RESEARCH

Five-year sunset clauses were included as part of the original FDAMA pediatric provisions, BPCA, and PREA bills because it was unclear at the time whether these measures would actually be able to achieve their intended goals of encouraging pediatric drug development. But after 10 years and two re-evaluations, it is abundantly clear that BPCA and PREA have not only achieved their intended goals, they have exceeded them, and millions of sick children and their families have already benefited as a result.

By removing the sunset clauses, Congress will remove the uncertainties created every 5 years and encourage the creation of a more sustainable infrastructure for pediatric drug development. Even despite all of the successes of BPCA and PREA in stimulating participation in pediatric drug development across companies of all sizes, the sunset clauses in them remain major hindrances, discouraging companies from formally organizing pediatric infrastructures.

By "infrastructure," I mean much more than merely brick, mortar, and layers of management. The building of sustainable pediatric drug development infrastructures from company to company and across the board means training people to be better researchers in pediatrics, developing new and better tools for measuring outcomes in pediatric clinical trials, and fine-tuning mechanisms of study to more fully and precisely account for the inherent heterogeneity of pediatric patients. Suffice it to say that this requires significant and sustained investment.

In the absence of a consistent and predictable exclusivity provision, there will remain a considerable and understandable reluctance among companies with countless competing research priorities to devote dedicated resources to formal pediatric divisions. This is especially true as the cost, size, number, and complexity of pediatric studies has increased and the absolute value of the pediatric exclusivity has decreased.

By removing the sunset clauses, Congress will convey a powerful message: Pediatric drug development is here to stay, and drug safety and effectivenesss for children is firmly among the Nation's highest priorities. The sunset clauses' removal will also help the advocates of pediatric drug development in industry to encourage their respective institutions to create and sustain the necessary infrastructure to continue improving pediatric therapeutics. Furthermore, it will provide a platform from which those companies that have made investments in pediatric drug development infrastructures can confidently increase those investments, including expansion into new research areas.

Every pediatrician knows that more pediatric studies are needed. You can help them get what they need.

CONCLUSION

In conclusion, there is no question that renewal of Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act—absent their sunset clauses—is vital to continued progress in the area of ensuring safe and effective medicines for children. No regulatory effort or legislation before these has come close to stimulating the kinds of advancements in pediatric drug safety and effectiveness that we've seen over the past decade.

I am confident that with the continuation of BPCA and PREA, we will see similarly sweeping advancements in this area for decades to come.

Thank you again, Mr. Chairman and the committee, for your tireless work on behalf of children's health and for giving me the opportunity to speak to you today. I look forward to answering any questions you may have.

Senator DODD. Thank you, Doctor, very much.

Dr. Campbell.

STATEMENT OF ROBERT CAMPBELL, M.D., PROFESSOR, DEPARTMENT OF ORTHOPEDICS, UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO, SAN ANTONIO, TEXAS

Dr. CAMPBELL. Mr. Chairman and members of the committee, thank you for this opportunity to testify today regarding safe medicine and medical devices for children. I am Dr. Robert Campbell, a pediatric orthopedic surgeon, an inventor and the father of five children. I am a Professor of Orthopedics at the University of Texas Health Science Center at San Antonio.

Throughout my career, I have cared for children in need of medical technology that was not readily available to them but the primary reason I was invited to appear before you today is that I both invented, developed and brought to market, a life saving pediatric surgical device known as the Vertical Expandable Prosthetic Titanium Rib, also known as VEPTR. This was approved as a Humanitarian Device Exemption device in 2004, after 14 years of FDA trials.

I am here to help provide you with some insight from someone who has been in the trenches and about how this pending legislation can help the children who need devices.

Children deserve access to devices that are safe, effective and made just for them but they are frequently denied access because there is a relatively small market for pediatric devices but little incentive for manufacturers to make them. We physicians must commonly jury-rig existing devices for children.

The VEPTR was invented to replace such a jury-rigged device that had been used to save the life of a 6-month-old full-time ventilator-dependent infant born with scoliosis and missing ribs. I made many mistakes in developing VEPTR. I had no experience in device development or knowledge of FDA requirements. I had no mentor. But learning through trial and error over the years, supported by grants from the National Organization of Rare Disorders and Orphan Products Division of the FDA and luckily, identifying child advocate manufacturers, we succeeded after 16 long years. Many hundreds of pediatric devices, however, have never been developed and probably won't be under current conditions but children deserve better.

I am here today to express my strong support of this bill and express my sincere gratitude to Senator Dodd and Senator Clinton for their commitment to achieving safe and effective medical devices for all children.

The following provisions address many of the obstacles we faced when developing the VEPTR device for children. This bill creates a contact point at the NIH and requires the FDA, NIH and the Agency for Health Quality and Research to work together on identifying important gaps of knowledge and improve pediatric medical device development.

An important component of this is the ability to survey the pediatric medical providers' rank and file in order to learn the actual unmet pediatric device needs. The bill also establishes 6-year demonstration grants to support nonprofit consortia to provide critically needed support in helping innovators with pediatric device ideas to navigate the system successfully and bring new pediatric devices to market. The consortium will mentor inventors and connect them to manufacturers and available Federal resources. It will also coordinate with the NIH contact point for pediatric device development and the FDA for facilitation of pediatric device approval.

The profit restriction on Humanitarian Device Exemption of approved devices has limited the effectiveness of the provision by forcing device manufacturers to only recover their research and development costs. By eliminating the profit prohibition for children, the bill increases the incentive for companies to manufacture pediatric devices, especially the small manufacturers who are likely to embrace an affordable pediatric device development pathway with definable, affordable regulatory requirements.

The bill will also result in improvements in the way the FDA tracks the number and type of devices approved for use in children and will strengthen postmarket safety.

I would like to thank the committee for allowing me the opportunity to share my support of the Pediatric Medical Device Safety and Improvement Act that will help future innovators to avoid my mistakes and my frustrations so that they can get their devices off the napkin and into the device shelf in a safe and timely fashion for the pediatric patients who need them.

I urge the members of the committee to support this legislation. I thank you for asking me to be here and I will be glad to address any questions you may have.

[The prepared statement of Dr. Campbell follows:]

PREPARED STATEMENT OF ROBERT M. CAMPBELL, JR., M.D.

Chairman Kennedy, Senator Enzi, and members of the committee, thank you for this opportunity to testify today regarding safe medicine and medical devices for children.

I am Dr. Robert Campbell, a pediatric orthopaedic surgeon, an inventor, and the father of five children. I am a Professor of Orthopedics at the University of Texas Health Science Center at San Antonio and hold the President's Council/Dielmann Chair in Pediatric Orthopaedic Surgery. I work primarily at Christus Santa Rosa Children's Hospital in San Antonio. I am a specialty surgical fellow of the American Academy of Pediatrics and serve on the Medical Advisory Committee of the National Organization of Rare Disorders. Throughout my career, I have cared for children in need of medical technology that was not readily available to them and my work has made me keenly aware of the need for better medical devices for children.

The primary reason I was invited to appear before you today is that I invented, developed, and brought to market a life saving pediatric surgical device known as the Vertical Expandable Prosthetic Titanium Rib (VEPTR), which was approved as a Humanitarian Device Exemption (HDE) device in 2004 after 14 years of FDA trials (see attached). I am here to help provide you with some insight about the problems of pediatric device development from someone who has "been in the trenches" and about how this pending legislation can help the children who need devices.

THE NEED FOR SAFE AND EFFECTIVE MEDICAL AND SURGICAL DEVICES FOR CHILDREN

Mr. Chairman, as a pediatric orthopaedic surgeon, I am very pleased to hear my colleague, Dr. Gorman, describe the gains made in the field of pediatric pharmacology as a direct result of actions taken by Congress. I support his view that the Best Pharmaceuticals for Children Act and Pediatric Research Equity Act are critical laws to children and must be reauthorized. But just as the need existed in 1997 when this committee and Congress acted to help children by increasing the study of drugs, Congress now has the opportunity to take the same kind of action with an equally important need: children's medical and surgical devices.

As a surgeon who has treated the orthopaedic diseases of children for over 20 years, I have been frustrated many times that the "shelves are bare" when I need a modern device for their care. A surgeon from the 1950s would recognize many of the pediatric instruments and devices in my operating room because there has been little progress. We pediatric sub-specialists are an endangered species, with less physicians each year choosing to join our ranks for complex reasons, especially in orthopaedics,[1 2] and one reason for this may be that we don't have the up-to-date technology to care for children that is available to our adult counterparts.

Children need medical devices that meet their unique needs. Devices for children should take into account their smaller size, accommodating their growing bodies and active lifestyles.

Children deserve access to devices that are safe, effective, and made just for them. Yet today many devices are not made with these considerations in mind, and some necessary devices are not made at all. Because pediatric disease is generally rare, there is a relatively small market for pediatric devices and there appears to be little incentive for device manufacturers to make them. Device manufacturers have different marketplace challenges than pharmaceutical companies. New medical and surgical devices quickly become obsolete, so large markets are needed to justify their development and regulatory costs. As a result, children are frequently denied access to the latest technology in life-changing or life-saving devices. Other times, physicians must "jury-rig" existing devices to accommodate their young patients.

But when children need a medical device that is unavailable, the consequences can be tragic. Twenty years ago, I became involved with a child that needed a pediatric device to survive that did not exist. Instead of accepting the inevitable, we decided to do whatever was necessary to provide him with a chance for life. None of us at the time had the slightest idea about how to develop a medical device, but since it was critically needed, we had to try it. None of us realized the ultimate cost of that decision, and how it would take 16 years from drawing the first blueprint to having an approved pediatric implant available on the "device shelf" for other surgeons to use. I wish to share what we learned through that experience.

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[1] Huurman W. Report of the Pediatric Orthopaedic Work Force Committee of the Pediatric Orthopaedic Society of North America. 2003.

[2] Bell MJ, Catterall A, Clarke NMP, Hunt DM. "Children's Orthopaedics and Fracture Care." Special Report. British Orthopaedic Association. July 2006.

THE TITANIUM RIB SAGA

The Vertical Expandable Prosthetic Titanium Rib (VEPTR) device, also known as the titanium rib, was invented to save the life of a 6-month-old full-time ventilator-dependent infant born with scoliosis and missing ribs.

In 1987, Dr. Melvin Smith, a pediatric general surgeon, was consulted by the family about tracheostomy care of this child. Although he was expected to die soon, Dr. Smith felt it might be possible to salvage the situation somehow and he asked me to get involved in a last ditch effort to save his life. There was no known commercially available chest wall prosthesis for this age group, and there was no way to stabilize his scoliosis without stopping growth of the spine. We managed to come up with a possible solution and, with nothing to lose, the family gave us permission to operate on the child as soon as possible. At surgery we "jury-rigged" an artificial chest wall of orthopaedic fracture pins, wired vertically to support the lungs and control the scoliosis. It was a difficult surgery, but to our amazement, it worked, and days later the infant was weaned off his ventilator for the first time and went on to be weaned off oxygen. We were very happy about the initial outcome.

But since our patient survived and was growing, we were now faced with new problems. The crude "jury-rigged" chest wall device would not grow with the patient, and the lung underneath would try to grow, but would eventually be compressed with adverse effect on its growth. The non-growing fracture pins would also tend to tether the growing spine and worsen the scoliosis. We could change out the crude device frequently in major surgery, but sooner or later we would have a catastrophic complication.

A new device had to be invented for this child and it needed to be safe to implant, just as effective as the "jury-rigged" device, but expandable in a simple fashion with minor surgery to avoid major complications. And it was needed quickly. I promised Dr. Smith that I could develop such a device with my engineering background, and assumed it would be an easy matter to get an orthopaedic manufacturer to make it. The confidence of the naïve is boundless.

The engineering blueprints of the first VEPTR device were drawn up 10 months later. It was a simple metal device with only two moving parts that could perform the same function as the fracture pin device, but was safer to implant and easy to expand as the child grew. I thought the job was mostly done at that point, but little did I realize that I had just made the first small step in a very long journey. I contacted multiple orthopaedic companies to make the device. They were sympathetic, but did not have the resources to make a pediatric device for one patient with a rare birth defect. I was getting discouraged as the months went by and the patient grew worse.

Finally, an orthopaedic custom device company, Techmedica Corporation of Camarillo, California, was recommended to me and they seemed receptive to making the device. Although they knew that making a completely new pediatric device would cause a substantial financial loss for them, with little hope of enough subsequent patients to recover development costs, they proved to be advocates for children and did accept the challenge. All they asked for in return was that, if the surgery proved to be successful, we would publicize their role in the surgery. We began an emergency effort to quickly produce a working device.

Six months later the first VEPTR device was manufactured and we successfully replaced our "jury-rigged" device with it in April 1989. When news of the new surgical device for rare birth defects of the spine and chest wall came out, we were inundated with desperate families trying to find treatment for their children. We were able to develop five new surgeries to help these children using the VEPTR device as its basis, but there was too much patient volume to continue treatment under the custom device provisions, so the FDA was approached for guidance. I was asked to provide a personal briefing for the FDA chief of devices. He was quite supportive of our efforts to develop a new implant for these lethal birth defects, and authorized a sole site FDA feasibility study which was began in 1991 with Techmedica Corporation as the sponsor.

Things went well for the next few years with encouraging clinical results. To their credit, members of the FDA permitted several minor modifications of the device by Techmedica Corporation during this time to enhance pediatric patient safety. This was cited by the 2005 Institute of Medicine Report "Safe Medical Devices for Children" as a favorable example of pediatric device development.

During this period we received critical seed grant funding from the National Organization of Rare Disorders to support our research. Based on the preliminary clinical trial results made possible by the NORD support, we were able to secure further substantial grant support from the FDA Office of Orphan Product Development

that enabled us to complete our sole site FDA study and initiate a multi-center FDA VEPTR trial.

A few years into the feasibility trial we were devastated to learn that Techmedica Corporation was to be closed by their large corporate parent. New patients needed VEPTR devices, and treated patients needed new larger devices because of growth, but we now had no way to provide them. We needed a new guardian angel to make the VEPTR, but had no idea where to find one. Incredibly, the angel found us.

Soon after the Techmedica Corporation closure, I was approached during an orthopaedic trauma course by a device product manager with the Synthes Spine Company, Mr. Paul Gordon, who was interested in knowing more about the VEPTR device. We soon learned he was a champion for pediatric patients. He convinced us that his company had the resources and the commitment to children to successfully take over the development of the VEPTR device. Through his efforts, I next met with upper management of the company and, eventually, the private owner of this major spine company, Mr. Hansjorg Wyss.

Mr. Wyss proved to also be an advocate for children and, although the device had little chance of producing a profit, he gave his full support in 1994 for the engineering refinement of the VEPTR device and for involvement of the Synthes in-house regulatory division in the design of a FDA VEPTR multi-center trial. A large investment was made to upgrade the VEPTR device to a more standardized design that was easier to implant, and the multi-center Synthes VEPTR trial began in 1996.

The first new hospitals to join the VEPTR FDA multi-center trial were Children's Hospital of Pittsburgh and then Boston Children's Hospital. Another five children's hospitals eventually joined the study. These hospitals provided additional experience with VEPTR treatment to confirm the San Antonio results of safety and effectiveness, and by 2001 there appeared to be adequate experience to consider an FDA application for approval, but in 2002 FDA brought up a concern that there were no controls for the VEPTR study. Subsequently a Humanitarian Device Exemption (HDE) application was filed by Synthes in 2003 with approval by the FDA on August 24, 2004, concluding the 14-year FDA study of the VEPTR device.

THE LESSONS LEARNED FROM THE VEPTR EXPERIENCE

I made many mistakes in developing this device over those 14 years. I had no mentor. I had no experience in developing a device from an engineering viewpoint. I had no knowledge of the FDA requirements for device development. It was basically a trial and error experience for many years.

I did not know which manufacturer was the best choice for VEPTR. Small companies can be responsive to small pediatric projects, but do not have large budgets for device development or the regulatory resources to secure FDA approval. Large publicly owned companies have those resources, but can't justify non-profit pediatric device projects to their stockholders. We were extremely lucky that we found companies who could be responsive to the needs of children in spite of the many obstacles. Many individuals at the FDA clearly were advocates for development of children's devices, but a clear and transparent regulatory pathway for VEPTR approval did not exist. I had limited knowledge about what financial resources were available for support of the VEPTR study. The grants of the National Organization of Rare Disorders and the Orphan Products Division of the FDA were crucial support for the success of the VEPTR trial, but additional resources would have been helpful for a study that eventually took 14 years to complete. There were numerous additional problems during the VEPTR trial that could have been better addressed if we had access to resources and mentorship, but they did not exist at the time.

The VEPTR pediatric device is now available for children only through hard work by many individuals across the United States, commitment of device manufacturers without regard for their economic well-being, and luck. Many hundreds of other pediatric devices have never been developed and probably won't be under current conditions. With what I have learned from the VEPTR experience, I have gone on to personally help mentor a handful of physicians trying to develop devices for children, but really a broad, expert, well-organized national system is needed for this. Children deserve better. Legislative and regulatory changes are absolutely necessary so that others do not have to have the same struggle as we did.

My chance to contribute to a new approach to pediatric device development began in June 2004, when I came to Washington, DC. from San Antonio to participate in a series of meetings hosted by the American Academy of Pediatrics, Elizabeth Glaser Pediatric AIDS Foundation, National Organization for Rare Disorders (NORD), the National Association of Children's Hospitals, and the Advanced Medical Technology Association (AdvaMed). The "stakeholder" meetings resulted in a series of recommendations for improving the availability of pediatric devices. Those

meetings were a key turning point in that they were the first broad-based dialogue that engaged stakeholders in all aspects of pediatric devices from health care providers, manufacturers, and Federal Government regulators.

Subsequently, the Institute of Medicine produced a strong report in 2005 entitled, "Safe Medical Devices for Children." The IOM found flaws in safety monitoring and recommended expanding the FDA's ability to require post-market studies of certain products and improving public access to information about post-market pediatric studies. IOM reported:

> [T]he committee must conclude that FDA has lacked effective procedures to monitor the fulfillment of postmarket study commitments. The agency has lacked a basic, searchable listing of devices for which further studies were specified as a condition of their approval for marketing. Furthermore, it has not maintained any system for systematically monitoring the status of these study commitments based on periodic reports or updates from either its own staff or sponsors.[3]
>
> FDA can ask for clinical studies prior to clearing devices, although clinical data are submitted for only a small percentage of devices that go through clearance. FDA cannot, however, order postmarket studies as a condition for clearance. It can (but rarely does) order studies subsequent to clearance through its Section 522 authority. Studies that are ordered subsequent to the approval or clearance of a device are limited to 3 years (which often means a shorter period of evaluation for most individual study subjects). This may be too short a period for certain safety problems or developmental effects to be revealed.[4]

In July of 2005, the American Academy of Pediatrics established the Task Force on Pediatric Medical Devices to work with Congress to advance legislation to meet medical and surgical device needs of children. I am pleased to be a member of the Task Force.

The recommendations produced by the stakeholder meetings in 2004 and the IOM report on device safety in 2005 point to the need for Congress to pass legislation that both stimulates device development and manufacture as well as increases the safety monitoring of pediatric medical devices, particularly after they are on the market. The Pediatric Medical Device Safety and Improvement Act 2007, S. 830, strikes the right balance and puts forward a comprehensive package that serves a critical step forward for children.

SUPPORT FOR THE S. 830, THE PEDIATRIC MEDICAL DEVICES SAFETY AND IMPROVEMENT ACT

I am here today to express my strong support of S. 830 and to express my sincere gratitude to Senator Dodd for his commitment to achieving safe and effective medical devices for all children. This legislation is the result of huge effort put forward by present and former members of this committee, patient and provider groups, and device manufacturers. This bill will help children get the safe medical and surgical devices they need by strengthening safety requirements and encouraging research, development, and manufacture of pediatric devices. The following provisions address many of the obstacles we faced when developing the VEPTR device for children.

Defining the Need for Pediatric Devices

The bill streamlines Federal agency processes by creating a "contact point" at the National Institutes of Health (NIH) and requires FDA, NIH, and the Agency for Health Quality and Research to work together on identifying important gaps in knowledge and improve pediatric medical device development. An important component of this is the ability to survey the pediatric medical providers' "rank and file" in order to learn the actual unmet pediatric device needs.

Facilitating Pediatric Device Development and Manufacture Through Mentorship

The bill also establishes 6-year demonstration grant(s) to support nonprofit consortia to provide critically needed support in helping the innovators with pediatric device ideas to navigate "the system" successfully and bring new pediatric devices to market. The consortium will match inventors with appropriate manufacturing partners, provide mentoring for pediatric device projects with assistance ranging from prototype design to marketing, and connect innovators with available Federal

[3] Field MJ and Tilson H., eds. Safe Medical Devices for Children, Committee on Postmarket Surveillance of Pediatric Medical Devices, Board on Health Sciences Policy; Institute of Medicine of the National Academies, 2005, p. 195.

[4] IOM, p. 226.

resources. The consortia will also coordinate with the NIH "contact point" for pediatric device development and the FDA for facilitation of pediatric device approval.

Improving the Humanitarian Device Exemption (HDE)

The Humanitarian Device Exemption (HDE) was meant to be a tool for approving devices intended for small populations (less than 4,000 patients), which often included children and those with rare conditions, but the profit restriction on HDE-approved devices limits the effectiveness of the provision by forcing device manufacturers to only recover their research and development costs. By eliminating the profit prohibition for children, the bill increases the incentive for companies to manufacture pediatric devices, especially the small manufacturers who are likely to embrace an affordable pediatric device development pathway with definable, affordable regulatory requirements.

Tracking Pediatric Device Approvals and Streamlining Device Development

S. 830 makes needed improvements in the way FDA tracks the number and type of devices approved for use in children or for conditions that occur in children. At present, FDA cannot satisfactorily produce data on the number and type of devices marketed for pediatric uses. The bill requires FDA to track new devices granted premarket approval or approved under the humanitarian devices exemption and report on the number of pediatric devices approved in each category.

STRENGTHENING POSTMARKET SAFETY

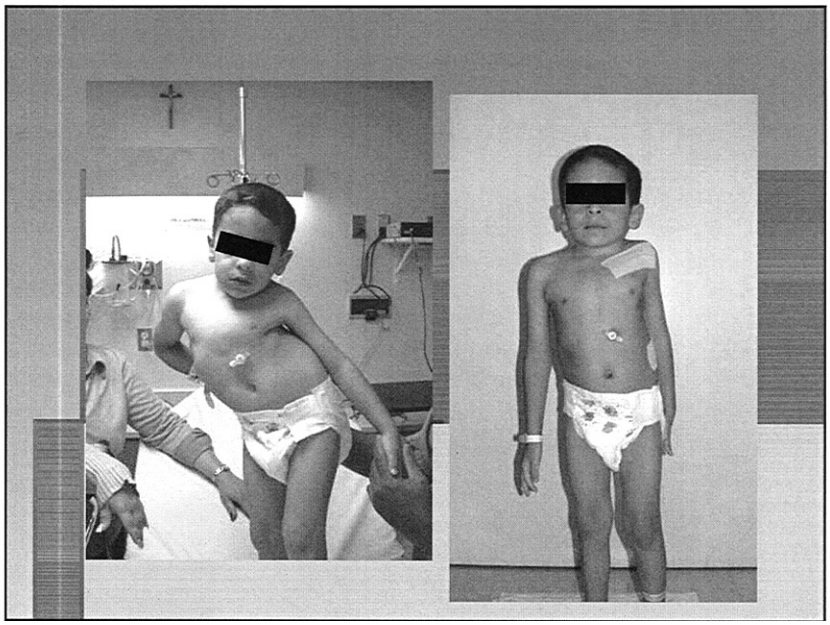
As recommended by the IOM, this bill grants the FDA increased authority to ensure that approved medical devices are safe for children. Under this law, the FDA would be able to require postmarket studies as a condition of approval or clearance for certain devices under section 522, if used significantly in children. This legislation also allows the FDA to require a study of longer than 3 years if necessary to ensure that the study is long enough to capture the effect of a child's growth on the safety and efficacy of a medical device. A database of such studies would be made available to the public. New postmarket authority can address the current limited amount of available data on devices for children and to create a mechanism for ensuring that needed pediatric studies are conducted for a sufficient length of time. The legislation is crafted so that there is no delay in approval or clearance for a device.

CONCLUSION

I would like to thank the committee for allowing me the opportunity to share my support of the Pediatric Medical Device Safety and Improvement Act, S. 830. This bill represents a historic step forward for children's medical and surgical devices similar to those steps taken on drugs. It will help future medical inventors of pediatric devices to avoid my mistakes and my frustrations so that they can get their devices "off the napkin" and into the pediatric patients who need them, in a safe and timely fashion.

I urge the members of the committee to support this legislation. I would be happy to take any questions you may have.

The Titanium Rib Development
1987-2005
-IOM Report, Safe Medical Devices for children, 2005



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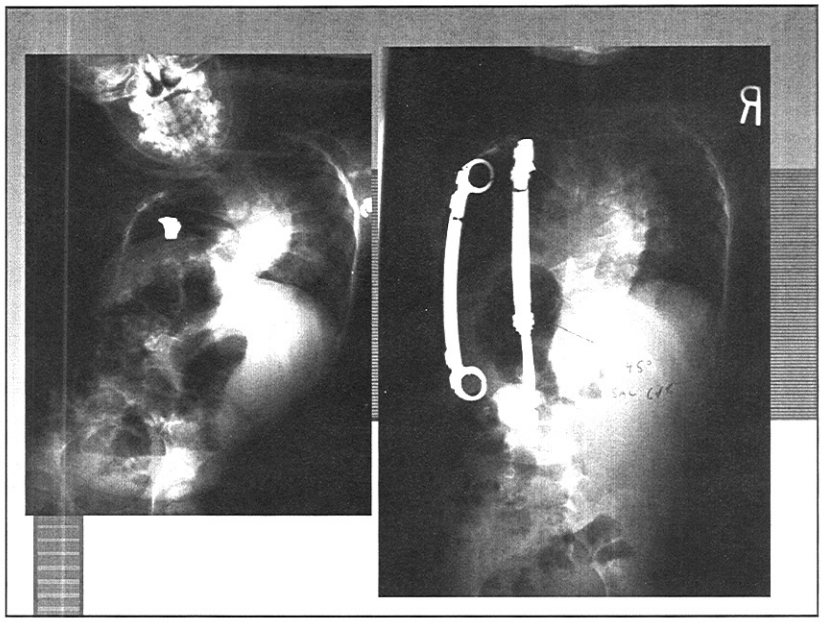

SUMMARY OF TESTIMONY

Chairman Kennedy, Senator Enzi, and members of the committee, thank you for this opportunity to testify today regarding safe medicine and medical devices for children.

I am Dr. Robert Campbell, a pediatric orthopaedic surgeon, an inventor, and the father of five children. I am a Professor of Orthopaedics at the University of Texas Health Science Center at San Antonio. Throughout my career, I have cared for children in need of medical technology that was not readily available to them, but the primary reason I was invited to appear before you today is that I both invented, developed, and brought to market a life-saving pediatric surgical device known as the Vertical Expandable Prosthetic Titanium Rib (VEPTR), which was approved as a Humanitarian Device Exemption (HDE) device in 2004 after 14 years of FDA trials. I am here to help provide you with some insight from someone who has "been in the trenches" about how this pending legislation can help the children who need devices.

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I am here today to express my strong support of S. 830 and to express my sincere gratitude to Senator Dodd for his commitment to achieving safe and effective medical devices for all children. The following provisions address many of the obstacles we faced when developing the VEPTR device for children.

The bill creates a "contact point" at the National Institutes of Health (NIH) and requires FDA, NIH and the Agency for Health Quality and Research to work together on identifying important gaps in knowledge and improve pediatric medical

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device development. An important component of this is the ability to survey the pediatric medical providers' "rank and file" in order to learn the actual unmet pediatric device needs.

The bill also establishes 6-year demonstration grant(s) to support nonprofit consortia to provide critically needed support in helping the innovators with pediatric device ideas to navigate "the system" successfully and bring new pediatric devices to market. The consortium will mentor inventors and connect them to manufacturers and available Federal resources. It will also coordinate with the NIH "contact point" for pediatric device development and the FDA for facilitation of pediatric device approval.

The profit restriction on Humanitarian Device Exemption (HDE)-approved devices has limited the effectiveness of the provision by forcing device manufacturers to only recover their research and development costs. By eliminating the profit prohibition for children, the bill increases the incentive for companies to manufacture pediatric devices, especially the small manufacturers who are likely to embrace an affordable pediatric device development pathway with definable, affordable regulatory requirements.

The bill also will result in improvements in the way FDA tracks the number and type of devices approved for use in children and will strengthen post-market safety.

I would like to thank the committee for allowing me the opportunity to share my support of the Pediatric Medical Device Safety and Improvement Act, S. 830. It will help future innovators avoid my mistakes and my frustrations so that they can get their devices "off the napkin" and onto the shelf in a safe and timely fashion for the pediatric patients who need them. I urge the members of the committee to support this legislation.

Senator DODD. Thank you, Doctor, very, very much and Mr. Rozynski, we thank you for being here as well.

STATEMENT OF ED ROZYNSKI, VICE PRESIDENT, GLOBAL GOVERNMENT AFFAIRS, STRYKER CORPORATION, WASHINGTON, DC.

Mr. ROZYNSKI. Thank you, Chairman Dodd, Senator Alexander and members of the committee. Again, my name is Ed Rozynski from Stryker Corporation. I am the father of three growing boys, one who reluctantly cut class today to be here to listen to the testimony.

[Laughter.]

Senator DODD. There will be a quiz at the end of this hearing.

Mr. ROZYNSKI. Senator Dodd, we sincerely appreciate your leadership role on children's issues and this landmark legislation. Like you and your colleagues, we want children to have access to the fullest and best medical treatments, even if that means doing or inventing something new just for them.

Stryker is one of the world's leading medical technology companies. We are the leader in orthopedics and in the other medical specialties. We have facilities around the country, in Massachusetts, New Hampshire, Tennessee, New Jersey, California, Michigan and Texas.

Stryker's products are used in over 80 percent of the hip and knee replacements performed in the United States each year. We are also involved in bone regeneration technology and it is now being used on soldiers at Walter Reed.

Stryker's commitment to children is not new. We are the leading manufacturer of orthopedic oncology prostheses in the United States and also craniofacial deformities, such as cleft lip and palate. We take very seriously our responsibility to ensure that our devices are safe and effective for use in pediatric patients. Soft tissue and bone cancers represent less than one percent of all adult

malignancies. However, they represent 15 percent of all malignancies in children.

Twenty years ago, the standard treatment for any primary malignant bone or soft tissue sarcomas was amputation of the affected arm or leg. Since that time, Stryker has partnered with leading orthopedic oncology surgeons to develop limb-sparing, surgical solutions, including growing prosthesis that can be elongated to account for a child's growth.

As with cancer, the treatment of craniofacial deformities is an area in which Stryker also has medical products and solutions. We sponsor and partner with organizations, including Operation Smile, a nonprofit organization dedicated to repairing childhood facial deformities around the world. Last year, Operation Smile was able to provide free cleft lip surgeries to more than 8,000 children in 23 countries. These surgeries only took about 45 minutes and costing $240 per child and they have a positive, lasting impact on the lives of the children and their families.

It is our sincere hope that this pediatric device legislation will spur the evolution of novel health care solutions for children.

Given Dr. Campbell's fine testimony, I won't go through the provisions of the bill except to say, we support the money that is going to be put aside for grant programs, including the match making between inventors and manufacturers. We support the incentives that could help to develop more pediatric products. We support the pooling of information for the pediatric database so solutions can easily be shared among us and analyzed so we can come up with better products.

In conclusion, Senator Dodd, we applaud you for introducing this legislation. We look forward to continuing to work with you on refining the bill and advocating for its passage into law this year.

As parents, we say that we give our children the very best. We protect them, we try to send them to the best schools. We buy them nice clothes and give them the latest and coolest electronic gadgets. Each one of us would walk though a wall for our children. Therefore, we should not allow children's health care products to become the residual of products that we develop for the big people that they look up to. Children deserve our very best efforts. Children deserve special attention.

At Stryker, we see the hope and the benefit that our latest bone implants provide to children with cancerous tumors. Unfortunately, many families, even those with health insurance, cannot afford to frequently take off work or pay the cost to travel with their sick child for regulator diagnosis and treatment in a far-away hospital. Stryker has decided that we will find a way to help provide charitable assistance to families and patients who are undergoing treatment for pediatric bone cancers at selected NIH Centers. We'd like to cover their expenses associated with such travel to these hospitals, expenses not covered by health insurance. These uncovered expenses often pose a serious impediment to a family's ability to provide for a child's care and recovery.

We believe that our planned, voluntary charitable initiative will complement the advanced medical technologies for children that Stryker already develops and that all companies will be further encouraged to develop as a result of your legislation.

Again, Mr. Chairman, I would be pleased to answer your questions or any that the committee may have. Thank you.

[The prepared statement of Mr. Rozynski follows:]

PREPARED STATEMENT OF ED ROZYNSKI

INTRODUCTION

Good afternoon. Chairman Dodd, Ranking Member Alexander, and members of the committee, my name is Ed Rozynski. I am Vice President of Global Government Affairs for Stryker Corporation ("Stryker"). On behalf of Stryker, an early supporter of this bill, I am pleased to present testimony today to support the "Pediatric Medical Device Safety and Improvement Act of 2007" (S. 830) and highlight the importance of ensuring the development of medical technologies for children.

Senator Dodd, we sincerely appreciate your leadership role on children's issues and specifically on this landmark legislation. Like you and your colleagues, we want children to have access to the fullest and best range of possible medical treatments, even if that means doing or inventing something new just for them.

STRYKER AND ITS COMMITMENT TO PEDIATRIC POPULATIONS

Stryker is one of the world's leading medical technology companies with the most broadly-based range of products in orthopaedics and a significant presence in the other medical specialties. Stryker Corporation is a Fortune 500 company with more than $5 billion in revenue and more than 17,000 employees. Stryker is committed to bringing the best possible solutions to patients, surgeons, and health care systems throughout the world. This philosophy has placed Stryker at the forefront of medicine's most promising breakthroughs in joint replacements, trauma, spine and micro implant systems, orthobiologics, powered surgical instruments, surgical navigation systems, endoscopic products, and patient handling and emergency medical equipment. Notably, Stryker's products are used in over 80 percent of the hip and knee replacement procedures performed each year in the United States.

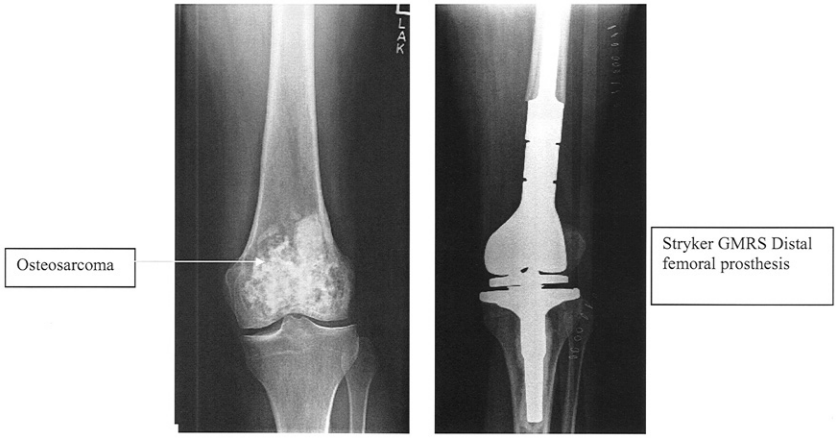
Stryker's commitment to children is not new. Our company is a market leader in products of significance for children. We are the leading manufacturer of orthopaedic oncology prostheses in the United States and have a significant presence in other medical specialties with a high percentage of pediatric cases, including craniofacial deformities such as cleft lip and palate. We also take very seriously our responsibility to ensure that our devices are safe and effective for use in pediatric patients.

I'd like to take a few moments to tell you about some of our products that are commonly used in children.

ONCOLOGY PROSTHESES AND CRANIOMAXILLOFACIAL TECHNOLOGIES

There has been significant progress over the past two decades in the management of patients with musculoskeletal cancers that has improved both the survival rates and quality of life of afflicted individuals. Soft tissue and bone cancers represent less than 1 percent of all adult malignancies; however, they represent 15 percent of all malignancies in children. Twenty years ago, the standard treatment for any primary malignant bone and soft tissue sarcomas of the extremity was amputation of the affected arm or leg. Since that time, Stryker is proud to have partnered with leading orthopaedic oncology surgeons to develop limb-sparing, surgical solutions, including the implantation of a growing prosthesis that can be elongated to account for a child's growth.

Often, a child's only chance to beat these aggressive forms of cancer is the removal of most, if not all, of an entire bone. Stryker's implant and instrument technologies are designed to allow not only for bone replacement with a prosthetic device but also soft tissue reattachment, which is critical to enable limb function following surgery. In children, there is often the need to have several surgeries to elongate the prosthesis to keep up with their growth, and Stryker provides solutions to meet this need.



As with cancer, the treatment of craniofacial deformities is an area in which Stryker also has significantly improved and broadened its range of available medical products and solutions. With continued innovation of craniomaxillofacial technologies, Stryker hopes to continue to transform the lives of children facing challenges such as cleft lip and palate.

We take pride in partnering with and sponsoring a range of medical organizations, including Operation Smile, a non-profit organization dedicated to repairing childhood facial deformities around the world. Last year, Operation Smile was able to provide free cleft lip surgeries to 8,531 children in 23 countries. These surgeries—on average taking 45 minutes and costing $240 per child—have a positive, lasting impact on the lives of pediatric patients and their families.

Finally, Mr. Chairman, I want to point out that children also suffer from other birth defects that, if left untreated, can cause permanent brain damage and/or severe disabilities. Craniosynostosis is a condition that results from premature fusion of the sutures or connections of the skull bones and has been estimated as a problem in 3 of every 10,000 live births. When this occurs, the pressure on a child's brain becomes an immediate threat to the organ's regular development. The surgical solution for this condition is deconstructing the skull and then reconstructing it to be normal in shape and size to permit normal growth. Stryker's Inion Baby™ system allows surgeons to effectively accomplish this procedure through polymer-based re-absorbable plates and screws specifically designed to re-absorb faster than the adult version of this product to accommodate the faster growth rates of children's bones. The Inion Baby™ system is also often used in cleft lip and palate surgeries.

PEDIATRIC DEVICE LEGISLATION

It is our sincere hope that the "Pediatric Medical Device Safety and Improvement Act of 2007" will further spur the evolution of novel health care solutions for children. This legislation provides a comprehensive approach for ensuring that children have access to medical devices that are manufactured with children's needs in mind.

First, the bill fosters the innovation of new pediatric devices. It authorizes new money to create a grant program to support the establishment of non-profit consortia to promote pediatric device development, including "matchmaking" between inventors and manufacturers. The bill also establishes a point of contact at the National Institutes of Health (NIH) to help innovators and physicians access funding for pediatric device development.

Second, the bill improves incentives for the development of devices for the pediatric market, which is very small. The cost of developing a new medical device and performing the required pre-market clinical studies can be enormous, often steering some manufacturers to serve larger, more established, and well known adult medical device markets.

Current law for Humanitarian Device Exemptions (HDEs) permits the Secretary of Health and Human Services to approve for use in up to 4,000 adults and/or children a year, a promising device that otherwise might not be approved. However, unlike for other FDA-approved medical devices, manufacturers are prohibited from making a profit on HDE products. The bill would lift the HDE profit restriction for

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new pediatric products only, in an effort to encourage more manufacturers to pursue the development of these products serving such small numbers of children.

Equalizing the incentives between pediatric HDE products and full market approval products in this way—even if the costs per patient are higher—likely will spur companies to develop pediatric products that they otherwise might not have. Moreover, these products might be targeted for pediatric populations with no other treatment options except through the HDE approval process. Therefore, it is important to provide incentives for surgeons, hospitals, and manufacturers so that they stick with innovative concepts for pediatric products to ensure that they make it from concept to reality.

Third, the bill facilitates the pooling and collection of more information about pediatric devices. Companies and other researchers are required to place certain pediatric postmarket studies and other research in a centralized, publicly available database so that information and solutions can be easily shared and analyzed. It also creates a mechanism to allow the Food and Drug Administration to track the number and type of certain higher-risk devices approved for use in children. In addition, the bill incorporates several recommendations made by the Institute of Medicine in its report on pediatric devices, including increasing the postmarket surveillance of medical devices used in children.

Senator Dodd, we applaud you for introducing this legislation and look forward to continuing to work with you on refining the bill and advocating for its passage into law this year.

CONCLUSION

In closing, I would like to say that Stryker is committed to working with others to find more and better solutions to the often costly and unique health care challenges of children.

We see the hope and the benefit that our latest bone implants provide to children with cancerous tumors. In order to reach more children, Stryker has decided that we will find a way to provide much-needed charitable assistance to families and patients who are undergoing treatment for pediatric bone cancers at selected NIH Comprehensive Cancer Care Centers in the United States. Specifically, we are looking for the best way to provide financial support for lodging, travel, and other nonhealthcare expenses associated with travel to a Center of Excellence hospital for treatment—expenses not covered by health insurance and that often pose a serious impediment to a family's ability to provide for a child's care and recovery.

We intend to finalize our plans and to announce them within the next several months, perhaps, in coordination with the passage of a much-needed pediatric device bill. We believe that Stryker's charitable initiative will complement the advanced medical technologies for children that Stryker already develops, and that all companies will be further encouraged to develop as a result of Chairman Dodd's legislation.

I thank the committee for the opportunity to testify this afternoon, and I would be pleased to answer any questions the committee may have.

Senator DODD. Thank you very much, Mr. Rozynski. We appreciate your work and we admire the work of the Stryker Corporation. We've passed here, back in 1993, the Family Medical Leave Act, which is unpaid leave but in the next coming few weeks, we're going to be introducing a paid leave program as well that would provide the resources, hopefully for a lot of people who need to be with their children.

I'll never forgot C. Everett Koop, the former Surgeon General of the United States testifying before this committee back many years ago when I first introduced the Family Medical Leave Act and telling this committee how the recovery rate of a child that has a parent or a loved one with them during a period of illness has just been well documented over the years and the ability to provide that opportunity for people to be together during those crises is absolutely immeasurable. So I appreciate the generosity and the idea of Stryker to be supportive of those families.

I'm going to put the clock on here ourselves and take about 5 or 6 minutes and turn to my colleague from Tennessee and my col-

league from Ohio, who has joined us and I thank you very, very much for your being here and your interest in the subject matter as well.

Let me turn, if I can, to Dr. Gorman. Some are suggesting that reducing the length of the pediatric exclusivity from 6 months to 3 months across the board and you addressed this already but I wondered if you might comment further on it and I may ask Dr. Maldonado as well, for any comments on this and you, Dr. Campbell, if you have thoughts on that particular subject matter.

Dr. GORMAN. The Academy wishes there to continue to be the flood of studies for children and the 6-month provision that was previously in the legislation provided such a flood. We also, however, are very aware that the 6-months of exclusivity causes an increased economic burden because it delays, in some people's minds, the institution of the generic form of that medication.

Reducing, as you presented in your introductory remarks, a lot of the drugs that went for exclusivity are, in fact, small market drugs, drugs that do not have large sales volumes when measured by the large pharmaceutical industry's measures of large, blockbuster drugs. To reduce those drugs to 3 months would, in fact, cut off the flow of studies. It would make it economically nonviable for manufacturers to do those studies without assuming too much risk.

Senator DODD. That's roughly about 80 percent of the companies we're talking about?

Dr. GORMAN. It looks like about 80 percent of the studies that—I'm sorry, of the drugs that were studied in the JAMA article. However, there are large drugs and blockbuster drugs that should be studied in children. Drugs become blockbusters because there are therapeutic advances or safety advances that should be shared by the entire population.

But the economic benefit to the pharmaceutical company that does those is much larger and could be restricted and still give pharmaceutical companies enough of a profit margin to take the risk of doing those studies as well as provide some financial relief for the rest of the population.

Senator DODD. Dr. Maldonado, any thoughts?

Dr. MALDONADO. Yes, Senator Dodd, we recognize that a different incentive has been proposed. Your 6-month exclusivity has worked very well and I am happy to report to you that companies have not cherry-picked only blockbusters. We've done studies across the board.

In my experience at J&J, what I've done to propose to my management to do pediatric studies and they know it well. I'm a physician, I'm a pediatrician. I'm going to come here in front of you, proposing development of drugs that are safe and effective for children or that I want to prove that are safe and effective for children, regardless of the economic incentive. In some of those drugs, you're going to have economic incentive. In others, you won't. But overall, this is our goal—to do what is right for children. Six months has worked very, very well. Going to 3 months will be quite a different experiment and this experiment for 10 years that you introduced 10 years ago and approved 5 years ago, has worked very, very well. A new experiment, we will have to see. But I am really very cau-

tious about entering a new experiment and see faders. This is a success and we should continue it.

Senator DODD. Doctor, do you have comments on this at all?

Dr. CAMPBELL. Maybe a few, Senator. It seems like the 6 months works. If it ain't broke, don't fix it. I'm a surgeon and I think a direct, simple approach is the best and I think, as Dr. Gorman and Dr. Maldonado has mentioned, there are some problems on the fringe that can be addressed separately.

Senator DODD. Well, 800 clinical trials is pretty significant. Those numbers blew me away. When we first introduced the legislation, going from 11 trials in 7 years, I thought we might get 20, might get 30 or 40 and I was going to consider that a pretty profound and significant number. When the numbers blew up and we saw that staggering number of tests being performed, it seemed to me that this was proving its value beyond anything we imagined when we introduced the legislation.

So again, I don't disagree with you. I'd be concerned as well as to what the implications would be. If this is doing its job and we're obviously trying to address the blockbuster issue here, which is a legitimate issue, in a way that strikes enough of a balance that we don't end up doing damage to what has been a rather miraculous development in terms of the products that are produced as a result of these trials. So I'll keep that in mind.

There have been some, Dr. Gorman—does the American Academy of Pediatrics support a clean authorization of BPCA? Someone suggested that and I, in my opening comments, made the point that this is an organic process here. With technology and other things that are occurring, I'd be tempted as the author of this legislation to see it become a permanent law and I've heard testimony of others who want that.

I've also watched enough changes occurring here that it's worthwhile for us to go back periodically and take a look at how we're doing in this area. So that's sort of my reaction to it. Tell me what the American Academy's reaction is.

Dr. GORMAN. Well, speaking for the American Academy of Pediatrics, we think the last bill was really good and we think the new bill, with the changes that have been introduced, will be even better—better for children and better for the health care that they have.

Voting for a clean reauthorization will overlook some of the problems logistically, of bringing the two programs closer together in a unified management inside the Food and Drug Administration. PREA and BPCA came from different roots and they have found different homes in the Food and Drug Administration that should, in fact, be unified so that all children's data that is presented to the Food and Drug Administration can be reported in a similar way, making it more transparent for both the regulatory agencies, the pharmaceutical industry and our caregivers, to understand the information that is coming out for kids.

So no, we would not support a clean reauthorization. We think that there should be changes to improve the statute.

Senator DODD. Thank you very much.

Senator ALEXANDER. Thank you. This is a good hearing to get to come to because it's not this often that Congress actually passes a

bill that works this well, it seems to me. I mean, this is very refreshing. He didn't hear the compliment but I'll—somebody will tell him later.

[Laughter.]

Senator ALEXANDER. But let me—I can——

Senator DODD. I heard the compliment.

Senator ALEXANDER. Well, I'm deaf ears here. I wasn't here——

Senator DODD. If you'd like to repeat it, go right ahead.

Senator ALEXANDER. I just said it's not often Congress passes a law that works this well. That's all I was saying. I wasn't here when it was passed.

So let me ask a couple of questions. If I'm understanding right, what we're saying is that this has been a really good thing, to have a fourth or a third of the drugs now available, tested for children, something like that and that it has worked pretty well. And that it has created a flood, is the word that has been used, of tests. If the flood is such a good thing and if the incentive encouraged a situation where—which is the number? Is it a fourth of the drugs or a third of the drugs that are now tested for children? Does anyone know the answer to that?

Dr. CAMPBELL. The number is in between those two numbers.

Senator ALEXANDER. About a third of all drugs that are available are tested for children? Am I saying that right? OK. Why shouldn't our goal be that two thirds or all drugs should be tested for children? And if giving a 6-month incentive created a flood of tests, would a 7-month incentive create a larger flood or an 8-month incentive create even more of a flood? Did you consider that when you considered your testimony today?

Dr. Gorman.

Dr. GORMAN. Where there is so much pressure to cut down the profits of pharmaceutical companies that nobody thought that was realistic.

Dr. CAMPBELL. The 6-month incentive was the result, in previous legislation, of a fair amount of compromise between different people with different length determinations and like many good Congressional policies, it was one that was picked as a compromise number and as you've already stated, worked quite well.

Senator ALEXANDER. Yeah.

Dr. CAMPBELL. As Dr. Maldonado has said in his testimony, one of the things that he wishes for the most is that he wishes the pediatric infrastructure for doing these studies to become permanent and secure and I share that dream. So I want an authorization of BPCA that continues to provide a steady stream, a steady flood of studies and I don't magically know the number that will give us the most. But the numbers we have so far do work and there is some evidence out there that by looking at economic studies and I'm not an economist—but when you look at the economic return for companies, the economic return for the blockbuster drugs could be limited and still give enough of a financial incentive for corporations to continue to pursue those studies for children.

Senator ALEXANDER. Yes. Well, you've testified that 6 months is fine in general but the blockbuster drugs—that profit might be reduced, was your conclusion. Did I get that right?

Dr. CAMPBELL. It could be reduced and still be enough of an incentive to continue to have companies do those studies.

Senator ALEXANDER. But I want to press this a little bit. I mean, it was a very bold move for the Congress and everybody that compromised and agreed that we're going to add 6 months to the wait for a generic drug, just to see if whether it might produce these tests and in fact, you got a flood of them. So if 6 months got a flood and if you think they all ought to be done, then why wouldn't you go to 7, 8, or 9 months and have a big flood? Dr. Maldonado, what would your response to that be? I'm not recommending that. I'm just asking why wouldn't we, after this experience?

Dr. MALDONADO. It's fair and we think that 6 months has worked and it continues to work and this is a process that we're going—I don't want to recommend any other higher number because I don't know if it is going to increase or double the flood. I just don't know and I don't want to be perceived to be greedy but people have focused on the blockbusters and a journal article of a month ago actually shows that there are some studies that are done in which private companies lose money and I can tell you from our company, some examples in which we——

Senator ALEXANDER. So your argument is that the profits of blockbusters help pay for the less profitable trials?

Dr. MALDONADO. Absolutely, absolutely.

Senator ALEXANDER. But—Senator Dodd, this will be my last question, in this round anyway. If we're really happy with the results and we see the need for more—well, would you agree that—what percent of drugs should be tested for children? Is it 100 or is it 75?

Dr. MALDONADO. It's not a 100 because there are some drugs that are for diseases that only occur in adults and so it is not 100 percent.

Senator ALEXANDER. Well, is it 50 or 60 or 70?

Dr. MALDONADO. That's a very good question and I have not counted that but I will, now that you ask the question, I'll get back to you. But it's a fair amount of drugs that will have an application. The only thing is that sometimes in the life cycle, we put drugs out there in the market and we don't understand all the potential—we understand that it is safe and effective for the indication they have—is it later in the life cycle that we discover that they may have an application for children. Even we, having the expertise in-house, learn with time that there may be some applications for children later. But yeah, it's not 100 percent but maybe—I don't know—probably 50 or 70 percent, something like that.

Senator ALEXANDER. Thank you. Senator Dodd, I think as we go through the legislative process—you've had such success with this legislation. I mean, in 5 years, we may want to talk about, is there a way we can get above 30 percent—just to some number. Maybe it's not within percentage, maybe it's some other way but is there a way to do that?

Senator DODD. Well again, certainly as I said earlier, we were stunned by the number of clinical trials that occurred immediately after the enactment of the legislation. We literally were talking about numbers that might have doubled or tripled the 11 tests that had been tried in 7 years. The idea that we'd get 800 in a decade

was breathtaking. And very candidly, the reason we went through the process is—this is a legislation body and you don't sit and write legislation really but what you're trying to do is strike balances. There are those here who are very much opposed to the 6 months of exclusivity and would be against the bill. So I was trying, at the time, along with my colleagues here, to strike a balance here that we felt would draw enough of the companies in to work on this, that would not allow gouging to occur here at the expense of consumers and we didn't have any answer to the question of whether or not 6 months would do it or not. This is not going to be easy to get this through both Houses of Congress in the coming weeks before these laws expire.

So I'd love to tell you there was some genius that showed up and said, I promise you that this number will get you what you want. Basically, it was a compromise to make sure we could enact the legislation. It's not more complicated than that and it's proved to be far more successful than we imagined and in fact, the good news has been as well, as far as I'm concerned, that a relatively small number of the companies have produced blockbusters in the sense here. The majority are coming out of smaller companies, if the JAMA reports and studies are accurate.

So again, I'd love to see—and I think we may get closer to more—a higher percentage of these products being tested for children. We seem to be on that path here and the risk we run of monkeying around with this, in my view, on one side of the equation is, if you try to add to that 6 months, you're going to lose a lot of people who won't support a piece of legislation. You eliminate it all together and you're going to lose a bunch of other people on that. So I'm trying to strike a balance here that not only reflects the technology and the evidence that we've produced over the last 7 years but also reflects the political realities I have to deal with here as a Chairman of a committee trying to produce a piece of legislation that can pass. Old practicalities come into play here on this.

Senator Brown.

STATEMENT OF SENATOR BROWN

Senator BROWN. Thank you, Mr. Chairman and thank you all for your testimony. I think it's not a question but Senator Alexander's comments, I thought, were interesting. I have a couple of ideas about that. I think it's not a question of drug company profits as much as it is, do we want to delay generics where insurance companies and individuals and government taxpayers have to pay more for these drugs as they get the extension.

Ten years ago, I was on the House—I was the Ranking Democrat on the House Energy and Commerce Committee, HELP Subcommittee and 10 years ago and 5 years ago, we faced this issue and passed the bill.

But there was something else going on 10 years ago at the same time and that was—the same committee in the House. It was considering doubling the NIH budget over a 5-year period. So we were enacting the pediatric exclusivity bill to encourage clinical trials and encourage more research and what that would mean for children. At the same time, we were doubling the NIH budget and

what that meant for medical research for children and everyone else.

We are still and we should reauthorize pediatric exclusivity. The NIH budget, as you know, has been flat and what that has meant for research, especially children's research, is a downgrading of our abilities in this country to do the kind of research we need to do.

I was just at Cincinnati's Children's Hospital, the second largest recipient of NIH dollars of any children's hospital in the country. There was some $90 million a year. They are finding, as are children's hospitals everywhere, that when they submitted a proposal to NIH, about one out of three proposals, one out of four proposals of 5 years ago was being accepted. Today, it's closer to one out of ten and when they get NIH dollars, they usually get a 20 percent discount from the dollars that they ask for and they get no adjustment for inflation during the course of the research they're doing.

So it seems to me that if—I mean, this whole issue is—Dr. Gorman, you've illustrated and Dr. Maldonado—all of you, is a trade-off in part, on access versus the importance of clinical trial and the JAMA article, I believe, said—the study 13 out of 59 of these were blockbusters. I don't know how many of the 46 remaining were hundreds of millions of dollars and how many were for small—literally small sales.

But we don't want to prevent access, obviously, to generics for sure—I mean, we want to do what we can that way but I have an idea that I'd just like to bounce off of all of you that might be able to kind of address two public health problems. One is pediatric—the whole issue of clinical trials for children, which is what we're here for today. The other is pediatric health care research and since we're not going to increase NIH funding the way that we should in this Congress because of—whatever the reasons—the cost of the war, the cost of the tax cuts—whatever the reasons.

Let me just bounce an idea that—an idea I'm working on and see what all five of you think about its workability. Drug makers, under this plan, conducting pediatric tests would have a choice. They could either choose to receive 3 months of additional market exclusivity or they could choose to receive the 6 months that they get under present law if they agree—if they opt for the 6 months, they have to agree to contribute, say 15 percent of the profits they earn during those 6 months, just from the profits from that drug alone, particularly if it is a blockbuster, it will be meaningful, 15 percent of those profits to a trust fund that would finance pediatric research centers, any one of a number of children's hospitals. I would argue Cincinnati but I would be accepting of any research hospital around the country that does pediatric research.

So it would deal with giving the incentives for those small companies that aren't making a lot on their extension. It would not mean many—well, 10 percent of their profits so it would mean very few dollars or no dollars. For the blockbusters, it would mean—they are putting a significant number of dollars aside. They are still getting an extension, 6 months and a blockbuster means a lot of money.

So my question—my offer to Senator Alexander on an additional month or two or how do you get the number from 30 percent or so up to the optimal of 60 or 70 or 90 is something we thought

about in the House 5 years ago in our committee and that is, you figure out what the cost of the research is and you reimburse two times, three times, four times—you basically give those companies that amount of money so you're paying for their research and then some. That might get us on some smaller companies somewhere, too. And I would be open to consider that, too.

But if you would all comment, any of you comment on the idea. The choice is 3 months or 6 months, 10 percent of the profits go into pediatric testing and pediatric research. Any of you? You're all overwhelmed, apparently.

[Laughter.]

Senator BROWN. And I know you haven't thought about it yet, so—I mean, you haven't had a lot of time to think about it.

Dr. GORMAN. Stop me from speaking so I will say that—only that one of the issues the Academy would have with that proposal is the complexity in its administration. Pharmaceutical companies are rightfully—they play their cards close to the vest about profits from any individual item. So if you're going to move forward with that, at least a suggestion would be to start looking at sales rather than profits, which can be more easily documented.

Senator BROWN. And a smaller percent, then. Thank you for that and I would add that if you talked and quoting another on the panel, the pediatric infrastructure to make it secure, to make it permanent, I think that these dollars would help us build an even better base in terms of being able to do that. Anybody else? Thank you.

Dr. MALDONADO. Yes, Senator, I think that the pediatric infrastructure is something that we have helped indirectly, for example, the PTLU—the pharmaceutical research units that are funded by NIH in part and we're developing that infrastructure in the hospitals. Remember that we don't do the research ourselves in our buildings. The research is done in universities and in places where the patients are.

My concern is similar to Dr. Gorman, and that is how to administer that kind of program and not damper the incentives. But we are all for increasing the infrastructure there. But the administration can be a problem and agree with you.

Senator BROWN. Others?

Dr. CAMPBELL. I would echo that. Something that is different—we don't know the agendas of the different players and there may be a corporate strategy, a pharmaceutical strategy where they are looking at profits in different areas. Right now, it seems to be very simple and then people can sort of put that on their long term thinking and come out with an outcome. But if we start getting—it's like our tax code. It gets real complicated and you just don't know where you're going to end at the end of the day. Once again, I'm a simple surgeon and if it's simple, I can usually get through the day.

Senator BROWN. Thank you. Did you want to add anything? Thank you, Senator Dodd.

Senator DODD. Senator Allard.

OPENING STATEMENT OF SENATOR ALLARD

Senator ALLARD. Mr. Chairman, thank you. I want to thank the panel for being here. I know you have to take time from your jobs and what not but this is important. And I would agree with my colleagues here that the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act seem to be working.

So my first question—I'm going to do this direct, both to you, Dr. Campbell and Dr. Gorman. My background is that of a veterinarian so I've treated an animal from the size of a parakeet to an elephant. But I can understand the differences—when it comes to pharmaceuticals, I can understand the differences in size and dosage and metabolic systems. But when we get to the devices and what not, if they are nonreactive in one species, from my experience, they are nonreactive in all the rest and it's just a matter of size, applying to that.

So the question I have is on the Pediatric Medical Device Safety and Improvement Act, if that were passed, what kind of impact would it have on practice today and perhaps manufacturing today, if you could each respond to that in your respective fields.

Dr. CAMPBELL. I think that's a very important question and your analogy of using dosages and cross reactivity in species is important. But let me talk as an orthopedic surgeon. A disease of infancy changes things—bone infection can cause severe damage to the hip because of blood supply. It's very fragile in that time frame and may cause permanent catastrophic disability. The same infection in teenagers is less catastrophic because the blood supply has changed within the hip. So there is so many areas of complexity right now that aren't really dealt with with devices.

Senator ALLARD. That could change the procedure but it doesn't necessarily change the device manufacturing, does it?

Dr. CAMPBELL. It would change how the device is used, the shape of it. In fractures of the hip, there are devices that could be made that could bypass the circulation and do a better job of immobilization. We're working on that.

Senator ALLARD. I see.

Dr. CAMPBELL. So these nuances that are very critical for these children aren't dealt with very well by the manufacturers yet. But if we give them some encouragement then I think they'll be able to work with us better and understand these problems.

Senator ALLARD. Dr. Gorman.

Dr. GORMAN. I think one of the incentives will be to address issues that become apparent when you use devices for children. An example from the more medical field but still a device was the incubators used for babies. When someone finally put a microphone inside them to find out how loud they were, you could hear what kind of resonance in the sound inside these incubators there was from the ambient noise surrounding them and when they realized the noise inside the incubator was louder than the noise outside the incubator, they redesigned them so to allow them to have more sonic separation from the ambient areas.

Those kind of issues, which wouldn't come up for—or an adult would complain that it was too loud, children have to have it measured and then there has be a will and the finance——

Senator ALLARD. That wasn't a factor so much of—I mean, that happened without this law. You realized what the best care was as soon as that came to light. I think the practice kind of changed, didn't it? You didn't actually need a law for that change to occur?

Dr. GORMAN. For that particular change where there are hundreds of thousands of incubators around the United States, I think that would be an easy change for a company to understand. It would make medical sense and financial sense. For devices that would be used less frequently, like tubes or masks to help babies breath—again, there would be, when you go to miniaturize something, sometimes it works very well in the sense you can just take something big and make it small but sometimes if you make it small, you exceed the limits of engineering as they presently are and having incentives or testing or grants to get prototypes built would be very important for the continued improvement of care for those children.

Senator ALLARD. Thank you for your responses. Mr. Maldonado, we've been hearing lately that the pediatric, pharmaceutical and device industry and the best practices of pharmaceuticals has been working because it's more of the carrot and stick approach. Do you think—could you speak to the need for sort of a carrot and stick approach?

Dr. MALDONADO. That's why I said in my testimony, Senator, that these two laws actually work synergistically because what happens is that if a drug has been studied in adults for any indication, the FDA can evoke PREA until they sponsor—even if they didn't have it in their mind, you must do studies in pediatric patients for that indication.

Now, BPCA, since this is an incentive, goes beyond that. So you come around a table and say, we're going to do this because we have to do it because FDA is requesting it but there are other opportunities for this drug in children. And we consult with many physicians around the United States, many experts and we came to a consensus that they are all opportunities and we pursue them, completely beyond the label, something that even has not occurred probably to the FDA and sometimes even to us as companies. But clinicians out there know and that knowledge is brought in-house and investments are going to go way beyond the label. And that's the beauty of both legislations and that's why I think they work so well.

Senator ALLARD. Is it Susan Belfiore?

Ms. BELFIORE. Yes.

Senator ALLARD. What are your thoughts about the Pediatric Medical Device and Safety Act, from your experience with——

Ms. BELFIORE. With the children?

Senator ALLARD. With the Elizabeth Glaser Pediatric AIDS Foundation and you've been a mother of some HIV positive children.

Ms. BELFIORE. Yes. I would say that thank God, we haven't had a lot of opportunities to use medical devices but I would say that the little bit that we have had—let me give you an example. When the children—as I said, go for blood work every 3 months and starting at a very young age. They were 2-years-old, 3-years-old, doing this. It made a huge difference whether or not there was a

butterfly to take their blood work—that small needle for those small veins.

They would kind of freak out when they would see someone come with these larger needles toward them and then the whole thing was traumatic and I would say, that's just one small instance where it made a difference in our lives. I can only imagine many of the other instances where medical devices could be used, where children—where physicians might have to use something for an adult and in that process, it might harm the child, just because there is not anything that is offered to them.

Senator ALLARD. Mr. Chairman, I want to be sensitive to your time but can I ask one more question?

Senator DODD. Go right ahead.

Senator ALLARD. OK. I would just like to hear from anybody on the panel on this question. Do you see any conflicts between how all three pieces of legislation we've talked about in this hearing are currently written or how they interact with one another? Do you see any problems with them? I assume that no response means you don't see any problems?

Dr. MALDONADO. Do you mean for the ones that are right now before——

Senator ALLARD. Yes, the reauthorization bills that we have here, which are two of them and then the other legislation sponsored by Senator Dodd on the medical devices. Do you see any problems with those, any one of those three pieces of legislation, as they're written or how they might inter-react with one another? Do you see a problem with that?

Dr. MALDONADO. We are examining those legislations as a team in my company and we're going to be working with Senator Dodd and others to address some of the issues that we see.

Senator ALLARD. OK. So you could be—you'll be giving us a written response on that?

Dr. MALDONADO. That's correct.

Senator ALLARD. OK and Mr. Chairman, how soon do you ask for a written response to be provided?

Senator DODD. Well, we're going to ask—in fact, we're going to keep the record open for 10 days, because obviously not all members showed up here today to be a part of the hearing. Many of whom are not here have a strong interest in the legislation. We'll be reviewing the testimony and we'll undoubtedly submit some written questions to our witnesses and I'd ask them to respond, if you could, within the next 10 days to those questions, assuming you get the questions promptly here, which I would urge them to do so we can include them in the record. I don't want to speak for the Chairman here or the Ranking Member of the full committee but I think the goal is to be looking at a markup of these bills some time toward the middle of next month. So we're talking about something maybe a little less than a month from now to actually be beginning the process of legislating in this committee. We have expiration dates coming up in September, so the idea is to get these up, out of the committee if we can and then of course, helping the leaders schedule them appropriately on the floor debate and discussion. The other body is also engaging in a similar process. So there is a sense of some urgency, time-wise, to move along. So it

will be important that if you get these questions from our colleagues, you are to respond to them as quickly as you can.

Senator ALLARD. Can you get that response to us in 10 days, do you think?

Dr. MALDONADO. Yes, we will.

Senator ALLARD. Very good. And we'll have some questions, too, Mr. Chairman. We'll submit those and ask that you respond within 10 days, if you would, please. Thank you very much.

Senator DODD. Thank you, Senator and let me just add—Senator Brown left the room but I want to point out his suggestion, his idea is not a new one but there are two problems I see with it and I say this as someone who has great respect for Senator Brown and his interest and concerns about the legislation. One is, something like that could be construed as a tax, if you start asking for a levy on companies in exchange for the 6 months of exclusivity. And second, my greater worry is not so much that one but the worry I would have that considering that so many of these products are coming out of smaller companies and it's going to be so important that we keep that small manufacturer in the game here and if they continue to be attracted to what we're talking about here as a way to have these tests and to produce these products. I'd be very worried that an additional burden, while not intended for them, would have the effect of discouraging them, the calculation being that it's too risky for us to do this if, in fact, we come out of it with marginal profits anyway and this reduces it further. That might be enough to persuade them not to engage and again, given the data we have up to now, at least based on independent studies that have been done, a significant number of these tests are coming out of the smaller companies. So I would be very uneasy about what the implications could be on those companies and their decision to go forward with this.

I have no difficulty at all in trying to get generic products out as quickly as we possibly can and what we've tried to do here is strike the balance on this. So there is nothing written in marble or concrete or stone about 6 months here but to parrot the remarks that have been made by the witnesses and others, it seems to be working and at this point here, I'd be reluctant over a period of 5 years, to change something that has produced pretty good results—in fact, I'd say fantastic results and the fears that others had at the outset about this providing a huge amount of profits in the blockbuster area have not proven to the be case up to now.

Now obviously, we want to watch this and I'm supportive of coming back 5 years from now to review where we are, to make a determination as to whether or not that is still going to be case.

Ms. Belfiore, I wanted to raise something with you because I was so fascinated by that book, your blue book over here, of all the records. What did you do before? Where did you go to get information to decide what medications to provide for your children? Or dosages of things? Who did you rely on for that?

Ms. BELFIORE. Well, in the beginning, with this virus, as you know, there is not very—no one really knew. So when I first brought the children into the country, of course, their infectious disease specialist I relied on. But I also read everything I could get my hands on. And since there was not much information on chil-

dren, I really went to the adult population and how is that being—how are they being treated?

I'll give you an example and sometimes it worked and sometimes, like I told you with Mihaela, it didn't work. But early on, the protocol for children with HIV was to give them AZT as a mono-drug and I read that what was happening is that even in adults at that time, those who were just taking AZT alone were not doing as well as maybe even some who were taking no medications at all. They were not living as healthy lives and they were dying faster. So I went to my specialist, my infectious disease specialist and my children have been put on it, when it first came into country and I said to him, I'd like your support in taking my children off this drug. And he said, of course. We don't know what is going on right now. We don't know. We're just doing the best we can.

So knowing is so important and for me to have these acts and all the work that everyone has put into these and these are not easy. To me, they sound complicated, these laws. But the fact that they are working and the fact that we would be able to get the information that we needed about the medications right there would be wonderful. I don't think parents have any idea, most parents out there. I have asked, do you know that three quarters of all drugs that are out there have never—medications—have never been tested for children? And they have no idea.

Senator DODD. I know.

Ms. BELFIORE. I didn't even know to ask when Mihaela was put on that cocktail of drugs, has it been tested for children? The thought never even crossed my mind.

Senator DODD. We had examples of this, by the way, because the assumption is, it's always the smaller dosage. We've actually had examples where actually a larger dose——

Ms. BELFIORE. That's the situation here.

Senator DODD. So the assumption that smaller people take smaller dosages, in fact, proved to be incorrect.

Ms. BELFIORE. Because they metabolize it quicker.

Senator DODD. Yeah, much more quicker. Well, we're going to keep at this and your testimony has been very, very helpful once again.

Ms. BELFIORE. Thank you.

Senator DODD. I'm delighted to see your children and your family here and I thank you, Dr. Gorman, Dr. Maldonado, Dr. Campbell, for your excellent work. Congratulations. Mr. Rozynski, we thank you as well, for your work and we'll keep the record open for a few days here and respond to these questions that may come up.

The committee will stand adjourned.

[Additional material follows.]

ADDITIONAL MATERIAL

PREPARED STATEMENT OF THE ADVANCED MEDICAL TECHNOLOGY ASSOCIATION (ADVAMED)

AdvaMed is pleased to submit this testimony in support of S. 830, the Pediatric Medical Device Safety and Improvement Act of 2007. We commend Senator Dodd for his advocacy on behalf of children and for his willingness to work with stakeholders in the development of the legislation. We believe the legislation will provide help in ensuring expanded access to medical devices for children. AdvaMed would like to continue to work with Senator Dodd and members of the committee to further improve and strengthen the legislation to enhance pediatric device access.

EXECUTIVE SUMMARY

AdvaMed member companies produce the medical devices, diagnostic products and health information systems that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. Our members produce nearly 90 percent of the health care technology purchased annually in the United States and more than 50 percent of the health care purchased annually around the world. AdvaMed members range from the largest to the smallest medical technology innovators and companies. AdvaMed member companies have and continue to develop devices for pediatric use that:

- are used extensively in pediatric populations,
- were developed specifically for pediatric populations, or
- were specifically redesigned for pediatric populations.

Recommendations to Improve Efforts to Develop Pediatric Devices. AdvaMed has a number of recommendations to amend S. 830 to improve and strengthen pediatric access which are summarized below and discussed more thoroughly in the full written statement.

Eliminate Duplicative Provisions:

- The proposed Section 522 language would give FDA the ability to require postmarket surveillance even if there is no public health concern.
- The proposed postmarket surveillance database will be expensive and costly for FDA to manage and maintain. Such studies should more appropriately reside in a device clinical trial registry.

New Pediatric Humanitarian Use Device Program:

- Provide the Secretary with authority to selectively raise the annual population cap for specific pediatric conditions when FDA determines the health of pediatric patients requires an increase.
- Allow existing pediatric HDEs to automatically qualify for the new pediatric HDE program to ensure that existing pediatric HDEs will remain on the market.

Make Better Use of Existing FDA Regulatory Tools: While maintaining the existing standard of safety and effectiveness, where appropriate FDA should:

- Use objective performance criteria (OPCs), historical controls or well-documented case histories as endpoints to show effectiveness.
- Allow the extrapolation of clinical data between different sizes of the same device based on engineering testing and other non-clinical data.
- Rely on non-clinical data for modifications of devices specifically approved for pediatric patient populations when such modifications are unrelated to changes in intended use.
- Allow the acceptance of 510(k) devices intended for adult populations with the same use as a pediatric device as predicates for the 510(k) pediatric device.
- Allow the acceptance—as an appropriate control for investigational pediatric devices—of devices intended for use in adult populations when such devices provide the only device-related means for treating, diagnosing or preventing diseases or conditions in pediatric patients and have become the standard of care for such patients.

Compassionate Use of Pediatric Devices:

- Require FDA to develop regulations that would allow manufacturers to distribute no more than 100 unapproved devices annually to pediatric patients when such patients are afflicted with diseases or conditions that affect too few patients annually to justify the expense necessary to achieve an approved device under the HDE program. Appropriate controls would be specified in statute.

INNOVATING FOR CHILDREN'S HEALTH

There are many challenges to pediatric device development which are described below. However, there are numerous devices already on the market that are used extensively in the pediatric population, or were specifically developed or redesigned for pediatric populations.

These include, among others: pediatric spinal fixation systems, downsized fracture fixation hardware, and total joint prostheses that can be lengthened; diagnostic cardiac catheters, therapeutic cardiac catheters, vascular grafts, pacemakers and heart valves; syringes with the greater dose accuracy required for some pediatric medications and medication delivery systems that are less invasive (such as nasal or intradermal delivery devices); incubators, respirators and warming blankets; glucose meters; enteral pumps; septal defect closure devices and hydrocephalic shunts (including those with anti-microbial coatings); tracheal stents; cochlear implants; and diagnostic tests that are specific for diseases that more frequently afflict children (e.g., rotavirus tests) and diagnostic assays with pediatric indications (e.g., Albumin BCG & BCP, Alkaline Phosphatase, Amylase, Calcium, Carbon Dioxide, Cholesterol, etc.). Many of these have entered the market via the 510(k) review process—without the need of large clinical trials.

WORKING TOGETHER TO DEVELOP PEDIATRIC DEVICES

AdvaMed has been actively engaged with other stakeholders on the issues surrounding pediatric device development for several years. In June, October and November 2004, AdvaMed participated in a series of 4-day-long stakeholder meetings to discuss and better understand pediatric device access issues and concerns. Stakeholders included FDA, the American Academy of Pediatrics, the Elizabeth Glaser Pediatric AIDS Foundation, the American Academy of Orthopedic Surgeons, the National Association of Children's Hospitals, the National Institutes of Health and the National Organization for Rare Diseases.

In August 2004, AdvaMed also submitted comments[1] in response to FDA's request for comments regarding barriers to the availability of pediatric devices and in response to the congressionally mandated Institute of Medicine's report on postmarket surveillance of pediatric medical devices. In 2005, AdvaMed participated in meetings with interested stakeholders (e.g., FDA, AAP and AAOS) to develop a template survey targeting three pediatric subspecialties (Cardiology, Pulmonary Medicine, and Neurosurgery). The goal of the survey was to identify important pediatric needs that could aid in formulating potential regulatory and legislative solutions.

One example of the need for continued dialogue among stakeholders was highlighted during the stakeholder discussions. Pediatric clinicians expressed concern that pediatric adverse events are not appropriately captured in FDA's adverse event database. When the FDA adverse event form (MedWatch Form 3500A) was distributed, the clinicians reported that hospital risk managers discourage reporting on the form. For manufacturers, the data provided in these MedWatch reports are critical to understanding the ongoing performance and safety of their devices in a variety of uses and patient populations. Information from these reports (along with other post-market surveillance activities) helps guide manufacturers on potential changes needed to mitigate the severity or frequency of adverse events. The information may also point to potential device changes to enhance clinical effectiveness and utility. Dialogue among key stakeholders about access to pediatric devices has resulted in progress but continued dialogue is required.

CHALLENGES TO PEDIATRIC DEVICE DEVELOPMENT

AdvaMed's engagement on the pediatric device issue over the past several years has helped us better understand the challenges the industry faces bringing new devices to children. Some of these are enumerated below.

• *Identification of Pediatric Market*: Importantly, a key barrier continues to be difficult in identifying and defining pediatric device requirements including the quantities of pediatric patients with unmet needs (which naturally varies by condition). The good news is that the recent focus on pediatric device access has resulted in a growing interest in serving the pediatric population. Recently, AdvaMed was contacted by an independent group that wants to re-engineer and optimize existing medical device technology for pediatric use. The group asked AdvaMed for pediatric market data—the type of data that would have been developed for three subspecialties by the template survey developed by stakeholders in 2005. More work, espe-

[1] *See* Docket No. 2004N–0254: *http://www.fda.gov/ohrms/dockets/dailys/04/aug04/082504/04n-0254-c00011-vol1.pdf.*

cially specific pediatric requirements, will be needed to transform this growing interest into real pediatric devices.

• *Technical Barriers*: There are numerous technical challenges associated with developing devices for pediatric populations. For example, not all devices function in the same manner when manufactured in the sizes needed for pediatric patients. Secondly, the fact that the pediatric anatomy is subject to change and shape, especially in younger patients, may limit the appropriateness of some devices intended for long-term use (e.g., permanent, weight-bearing implants). In addition, the selection of materials used in pediatric devices must take into account the different susceptibility of children to physical and chemical agents. The metabolic and hormonal changes children experience during growth may also need to be taken into account. These factors can limit the range of materials from which pediatric devices can be fabricated, complicating design challenges. Other technical issues manufacturers must consider include the array of sizes needed to meet pediatric needs, the likelihood of patient compliance with limitations associated with devices and the ability to anticipate the activity level and forces imposed by patients who may not be able to or willing to exercise significant self-control.

The nature of establishing safety and effectiveness in pediatric populations is also different in devices than it is in drugs. This is not to say that many drugs don't require testing or reformulation for use in pediatric populations. However, for some devices, additional complexity can be introduced when defining test methodologies to demonstrate safety and effectiveness in pediatric populations. For example, separate animal testing in younger or smaller animals, along with the documentation and verification of the data for each separate model may be required. There are also technical challenges associated with retooling existing manufacturing lines or introducing new manufacturing lines (distinct from those used for adult devices) which may be required for many pediatric devices and models. All of these factors can add research and development complexity and cost.

• *Small Pediatric Market Size*: It is likely that for some pediatric device needs, the annual market will not be commercially viable for device companies. The complexity and cost associated with pediatric device development can be higher as noted above and yet manufacturers will in some cases be developing the device for a far smaller market.

• *FDA Regulatory and Data Requirements Can Discourage Pediatric Device Development*: FDA data and regulatory requirements can necessitate large pediatric clinical studies or require multi-year, multi-hospital studies with long-term results monitoring. Challenges include accruing sufficient clinical trial participants over a reasonable timeframe and within a manageable number of investigational sites to meet FDA requirements. For small populations of pediatric patients, the costs associated with conducting such trials may not be recouped. Further, for some pediatric conditions, the co-morbidities associated with the condition can make it extremely difficult to establish the effectiveness of the device. The clinical trial of a device that diagnoses or treats such a condition would likely experience many adverse events related to the co-morbidities making it difficult to assess the therapy under evaluation and generate enough data to establish the safety and effectiveness of the device using traditional clinical trial methodologies.

• *Perception of Potential Liability Risks Associated with Pediatric Device Use*: Finally, it is an unfortunate reality that the same conditions that have led to decreased availability of affordable malpractice insurance for pediatric surgeons has effects for device manufacturers. The perception exists that the financial liability arising from litigation involving a pediatric population is substantial and far greater than actions involving adult populations. The perception also exists that there may be an increased risk of liability associated with clinical trials involving pediatric conditions with many co-morbidities and congenital anatomic anomalies.

ADVAMED RECOMMENDATIONS TO FURTHER IMPROVE ACCESS TO PEDIATRIC DEVICES

AdvaMed recommends the following additions and changes to S. 830 to help improve pediatric access to existing devices and increase the number of cleared and approved pediatric devices.

• *Eliminate Duplicative Provisions:* We believe the proposed 522 language in S. 830 is unnecessary. FDA already has authority to require postmarket surveillance for any device raising a public health concern. The proposed language would give FDA the ability to require postmarket surveillance even if there is no public health concern. This is unnecessary given FDA's current broad, statutory authority and it may also discourage manufacturers from pursuing pediatric uses so as to avoid costly and unnecessary postmarket surveillance studies.

Congress amended section 522 of the Federal Food, Drug, and Cosmetic Act in the Food and Drug Modernization Act of 1997 to give FDA expanded authority to require postmarket surveillance or longer studies when issues arise after a product has been cleared or approved. The existing 522 statutory criteria are quite broad and can already be applied to products that are expected to have significant use in pediatric patients. In fact, FDA itself has claimed broad authority under the FDAMA 522 language. In its recently released "Guidance for Industry and FDA Staff—Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act," FDA says the criteria it will use to determine whether to impose postmarket surveillance is "*the delineation of an important unanswered postmarket question about a marketed device.*"

Finally, S. 830 requires FDA to develop a detailed post-market surveillance database. FDA is already developing a Web site for 522 studies. In addition, it is our understanding that the provision in S. 484 on clinical trial registries will be expanded to establish a registry for device trials, including postmarket surveillance studies. The proposed post-market surveillance database will be an expensive and costly proposition for FDA to manage and maintain. FDA has limited resources which are currently being supplemented by industry user fees. FDA's limited resources are more appropriately focused on other priorities.

• *Improvements to the Proposed Pediatric HDE Program*: AdvaMed supports the provision in S. 830 to add a pediatric-specific Humanitarian Device Exemption (HDE) program to the existing HDE program. The goal of this new program is to ensure pediatric access to needed devices. However, because there continues to be little information on the size of pediatric populations associated with specific conditions, it is unknown what affect applying the general HDE annual population cap of 4,000 (for designation as a Humanitarian Use Device (HUD)) to children's devices may have on the availability of devices to treat pediatric conditions.[2] AdvaMed recommends the Secretary be given authority to selectively raise the cap for specific pediatric conditions when FDA determines the health of pediatric patients requires an increase in excess of the annual distribution number—based on medical, demographic and scientific information provided by a petitioner.

AdvaMed believes that selective and careful raising of the cap for HUD designation is unlikely to be abused as a "shortcut" path to market by medical device manufacturers. The HDE program currently requires a manufacturer to provide evidence of safety to FDA as well as likelihood of effectiveness—before FDA will grant an exemption. Further, under current HDE regulations, a manufacturer seeking an HDE must demonstrate that no comparable devices are available to treat or diagnose the disease or condition and that they could not otherwise bring the device to market. Furthermore, FDA currently actively wields its authority to withdraw HDEs as witnessed by FDA's recent HDE withdrawals.

AdvaMed also believes that existing pediatric HDEs should automatically qualify for the new pediatric HDE program to ensure the continued availability of these HDEs and so as not to disadvantage those companies who have previously made significant investments in the development of pediatric HDEs. Not doing so may lead to voluntary withdrawals from the HDE program.

• *Make Better Use of Existing FDA Regulatory Tools:* S. 830 includes an important reminder to FDA that it should use certain valid scientific evidence mechanisms at its disposal in order to improve pediatric device access. Specifically, the bill reminds FDA that it may use adult data to support a determination of reasonable assurance of safety and effectiveness and that it may extrapolate between pediatric subpopulations where appropriate. AdvaMed recommends that the legislation be expanded to include other, similar types of valid scientific evidence mechanisms.

FDA frequently utilizes valid scientific evidence other than well-controlled trials, but is reluctant to take advantage of some types of valid scientific evidence in the case of pediatrics. We believe that highlighting FDA's existing statutory and regulatory authority to utilize other forms of valid scientific evidence i.e., other than evidence from well-controlled trials, by explicitly reiterating this authority in pediatric device legislation—as Senator Dodd did with the extrapolation of adult data—will encourage FDA to accept such data when appropriate and result in more cleared and approved pediatric devices. Encouraging CDRH to make use of all forms of valid

[2] An Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. To obtain approval for an HUD, an humanitarian device exemption (HDE) application is submitted to FDA. An approved HDE authorizes marketing of the HUD. However, an HUD may only be used in facilities that have established a local institutional review board (IRB) to supervise clinical testing of devices and after an IRB has approved the use of the device to treat or diagnose the specific disease.

scientific evidence is also responsive to the extremely small numbers of pediatric patients with any one condition or disease state (which makes it difficult to accrue adequate clinical trial populations in a timely fashion). It will also help minimize the use of pediatric surgical interventions as the control, especially where numerous articles document the effectiveness of a particular off-label use of a device and it has become the standard of care. In some instances, particularly surgical interventions, doctors are reluctant to randomize pediatric patients to a control arm if the off-label use of the device is the pediatric standard of care. This barrier prevents the off-label use of the device from ever becoming on-label.

AdvaMed's recommended statutory language would retain and emphasize the existing standard of reasonable assurance of safety and effectiveness. Importantly, under AdvaMed's language, FDA would retain full control. Where FDA has specific concerns, nothing would require FDA to clear or approve a device utilizing any of these forms of valid scientific evidence. See the attachment for a full description of AdvaMed's proposals in this area.

• *Establish New Compassionate Use Pediatric Device Provision:* During the 2004 pediatric stakeholder meetings, pediatric clinicians repeatedly reported that they felt compelled to "jerry-rig" or modify existing devices to treat pediatric patients. While FDA has a custom device program intended to address this problem, manufacturers have been reluctant to participate because the rules are unclear and custom devices are limited to just a few patients. AdvaMed has heard from manufacturers that they, on occasion, are compelled to choose between complying with FDA requirements *and* pediatric patients with the knowledge and heavy burden that their decision to adhere to FDA requirements may result in a dire outcome for the child. Based on available information, it appears these situations are not infrequent. Unfortunately, the Dodd legislation does not address this critical situation.

Rather than having pediatric clinicians across the country individually jerry-rig devices during surgery AdvaMed proposes a well-regulated mechanism to provide device access for super-small, pediatric, orphan populations that are not likely to be served by the proposed pediatric HDE program. AdvaMed recommends that FDA be required to develop regulations that would allow manufacturers to distribute no more than 100 unapproved devices annually for pediatric patients when such patients are afflicted with diseases or conditions that affect too few patients annually to justify the expense necessary to achieve an approved device under the HDE program. Appropriate controls would be statutorily mandated including: (1) compliance with quality system, labeling, adverse event reporting, device tracking and post-market surveillance regulations; (2) device promotion would be limited to medical professionals and no claims of safety or effectiveness could be made; (3) the manufacturer would be required to notify the Secretary upon the first shipment of such a device; (4) maintenance of records of each shipment of such a device; (5) limitation of distribution to prescription use only; (6) institutional review board approval would be required for each use of such a device; and (7) informed consent prominently informing the patient and the patient's parent or legal guardian that the device not approved by the United States Food and Drug Administration would be required.

In conclusion, AdvaMed looks forward to continuing to work with Senator Dodd and committee members toward consideration and approval of strong pediatric legislation to enhance pediatric device access.

ATTACHMENT.—ADVAMED PROPOSALS INTENDED TO MAKE BETTER USE OF EXISTING FDA REGULATORY TOOLS TO ENHANCE PEDIATRIC ACCESS TO MEDICAL DEVICES

For each of the proposals below, AdvaMed's recommended statutory language would retain and emphasize the existing standard of reasonable assurance of safety and effectiveness. Further, under AdvaMed's recommended language, FDA would retain full control—nothing would require FDA to clear or approve a device utilizing any of these forms of valid scientific evidence.

1. **Proposal:** Where appropriate FDA should use objective performance criteria (OPCs), historical controls or well-documented case histories as endpoints to show effectiveness.

Background: Reliance on well-documented case histories and historical controls would take advantage of the existing literature, respond to the extremely small numbers of pediatric patients with any one condition (which makes it difficult to run statistically valid clinical trials in a timely fashion—as one person put it "20 years of literature vs. years to put together a control group") and help minimize the use of surgical interventions as the control where devices have been established as the standard of care..

2. **Proposal:** Extrapolation of clinical data between different sizes of the same device based on engineering testing and other non-clinical data.

Background: Currently, FDA requires clinical evidence on the full range of device sizes for a particular device and it can be difficult to assemble enough patients at either end of the size ranges to be valid. It is extremely challenging to get data on the smaller and larger sizes. This proposal would allow the use of non-clinical and bench data to approve the full range of sizes.

3. **Proposal:** Reliance on non-clinical data for modifications of devices specifically approved for pediatric patient populations, when such modifications are unrelated to changes in intended use.

Background: Modifications are frequently made to devices (e.g., material changes, etc.). Every time a modification is made to a device (e.g., material changes or minor design changes), FDA has often required that the device be cleared or approved again. The requirements for clinical data in this process limit improvements for pediatric devices. Due to the challenges associated with gathering clinical data for pediatrics (small populations, parental unwillingness to have children participate, timeliness, etc.), the intent of this provision—for devices specifically approved for pediatric use—is to enable use of engineering and bench testing, rather than clinical testing for minor device changes when the changes are not related to the intended use of the device. FDA has the flexibility to do this, but should be specifically encouraged to do so in the case of pediatric products.

4. **Proposal:** The acceptance of 510(k) devices intended for adult populations with the same use as a pediatric device as predicates for the 510(k) pediatric device.

Background: Similar to the language proposed in the Dodd legislation which allows FDA to use adult data to support a reasonable assurance of safety and effectiveness in pediatric populations and to extrapolate data between pediatric populations, this provision would give FDA the authority, where the course of the disease or effect of the device is the same in adults and in pediatrics, to use the adult 510(K) device as a predicate for the pediatric device. It is intended to be responsive to the extremely small numbers of pediatric patients with any one condition (which makes it difficult to run valid clinical trials in a timely fashion) and to help limit the number of children exposed to surgical controls. FDA can still require a clinical trial for a 510(k) device but the trial would be smaller and the time to market would be faster.

5. **Proposal:** The acceptance—as an appropriate control for investigational pediatric devices—of devices intended for use in adult populations when such devices provide the only device-related means for treating, diagnosing or preventing diseases or conditions in pediatric patients and have become the standard of care for such patients.

Background: Similar to the language proposed in the Dodd legislation which allows FDA to use adult data to support a reasonable assurance of safety and effectiveness in pediatric populations and to extrapolate data between pediatric populations, this provision is intended to provide FDA with authority to utilize as the control for an Investigational Device Exemption, devices that are not approved for pediatric use but that are already being used in pediatric populations. This would enable the adult data on already approved devices or these devices themselves to serve as the "control" for the pediatric trial, responding to the limited number of pediatric patients available for pediatric trials and reducing the number of children exposed to a surgical control.

PREPARED STATEMENT OF THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA (PHRMA)

The Pharmaceutical Research and Manufacturers of America (PhRMA) appreciates the opportunity to provide a written statement for the record regarding the reauthorization of the Best Pharmaceuticals for Children Act (BPCA). PhRMA is the Nation's leading trade association representing research-based pharmaceutical and biotechnology companies that are devoted to inventing new, life-saving medicines.

HISTORY OF PEDIATRIC EXCLUSIVITY PROGRAM

Historically in the United States, significant disincentives existed to conduct clinical trials for pediatric use (generally speaking under the age of 16) of a medicine developed primarily for adult use. Among other factors, exposure to product liability and medical malpractice were prominent disincentives. Prior to enactment of the pediatric exclusivity provisions in the Food and Drug Modernization Act of 1997 (FDAMA), there were concerns that many FDA-approved drugs had not yet been clinically tested in children. For example, about 70 percent of medicines used in

children had been dispensed without adequate pediatric dosing information.[1] Growing recognition of the need for pediatric-specific information prompted action by Congress and the U.S. Food and Drug Administration (FDA).

Congress responded by providing incentives to encourage manufacturers to conduct pediatric studies of medicines with potential uses as medicines for children. FDAMA included a provision that granted pharmaceutical firms a 6-month pediatric exclusivity upon the completion of studies on the effects of a drug upon children that meet the terms of a written request from FDA. The 6-month period begins on the date that the existing patent or data exclusivity protection on the innovator drug would otherwise expire. Pediatric exclusivity encompasses any drug product with the same active ingredient. Although FDAMA included a sunset provision effective January 1, 2002, Congress subsequently reauthorized these provisions in the BPCA in 2002. The BPCA sunsets on October 1, 2007, unless reauthorized.

The BPCA, like the statute as it operated prior to passage of BPCA, provides a voluntary incentive to pharmaceutical companies of 6 months of marketing exclusivity for conducting pediatric studies of drugs that the FDA determines may be useful to children. The FDA can issue requests for pediatric studies of both on- and off-label uses of a drug. In order to qualify for pediatric exclusivity, FDA must first issue a written request for pediatric studies. An FDA written request contains such information as the indications and number of patients to be studied, the labeling that may result from such studies, the format of the report to be submitted to the FDA, and the timeframe for completing the studies. Response to the written request is voluntary. The pediatric studies must be completed by the deadline specified in the FDA's written request and submitted in the form of a new drug application (NDA) or a supplement. Six months of pediatric exclusivity is granted if the studies conducted "fairly respond" to FDA's written request and are conducted in accordance with "commonly accepted scientific principles and protocols." Also as part of the 2002 reauthorization, a new fund was established at the National Institutes of Health to support the study of off-patent drugs, which are not eligible for the incentive.

In addition to the BPCA, the Pediatric Research Equity Act (PREA) gives FDA the authority to require studies of drugs for the on-label indication only, i.e., when the use being studied in children is the same as the approved adult indication. PREA gave FDA the authority to require manufacturers to conduct pediatric testing for certain new drugs and biologics and produce formulations appropriate for children, e.g., liquids or chewable form tablets. PREA applies to products that are already on the market only if FDA determines that the absence of pediatric labeling poses a significant threat *and* after it exhausts the possibility of funding the pediatric studies through other public and private sources. In addition, PREA also applies only if the product is likely to be used in a substantial number of children and represents a meaningful benefit over medicines already on the market.

PEDIATRIC EXCLUSIVITY PROGRAM HAS GREATLY ADVANCED MEDICAL CARE OF CHILDREN

The pediatric exclusivity program has been a tremendous success. According to FDA, the current pediatric exclusivity program has done more to spur research and generate critical information about the use of medicines in pediatric patients than any other government initiative.[2] For example, by the end of 2006, FDA had issued 336 written requests for 782 pediatric studies involving 46,000 children.[3] In comparison, between 1990 and 1997, only 11 products were studied in children.[4] Moreover, the drugs studied under BPCA are used to treat more than 17 broad categories of diseases in children.[5] And one of the most devastating diseases in children—cancer—was the most prevalent disease category for which drugs were studied under BPCA.[6]

The public health benefits of these developments are undeniable. According to the American Academy of Pediatrics, "Pediatricians are now armed with more informa-

[1] U.S. Pediatric Studies Incentive Led to New Labeling for Nearly 100 Drugs, Impact Report, Tufts Center for the Study of Drug Development, Vol. 7, No. 4, July/August 2005.

[2] The Pediatric Exclusivity Provision, January 2001 Status Report to Congress," FDA, 2001.

[3] Pediatric Study Costs Increased 8-Fold Since 2000 as Complexity Level Grew, Impact Report, Tufts Center for the Study of Drug Development, Vol. 9, No. 2, March/April 2007.

[4] Jennifer Li, et al., "Return of Clinical Trials Performed Under the Pediatric Exclusivity Program," *JAMA*, Vol. 297, No. 6, February 7, 2007.

[5] Pediatric Drug Research: Studies Conducted under Best Pharmaceuticals for Children Act," GAO–07–557 (March 2007), at 5.

[6] *Id.* at 21.

tion about which drugs work and what doses."[7] Likewise, a February 2007 study published in the Journal of the American Medical Association (JAMA) found that, "The exclusivity program . . . represents a unique opportunity to expand our knowledge of the safety and efficacy of products used in children." The study concluded, ". . . the greatest return of the exclusivity program is the benefits derived in obtaining new information relevant and applicable toward the care of children, and this benefit should not be compromised."[8]

So far, the completed and ongoing studies have resulted in the development of new formulations to cover additional and younger patients and the development of novel clinical trial designs and tools to evaluate safety and effectiveness. Requests for studies have been made in a wide range of therapeutic areas, including treatment of fever, skin conditions, heart disease, HIV, seizure, cancer, endocrine problems, gastrointestinal disorders, and more. According to a recent U.S. Government Accountability Office (GAO) report, the most frequently studied drugs were those to treat cancer, neurological and psychiatric disorders, metabolic diseases, cardiovascular disease, and viral infections. GAO also found that nearly half of the 10 drugs most frequently prescribed for children have been studied under the BPCA.[9] The range of conditions addressed, the variety of drugs being studied and the nature of the scientific data all confirm that the pediatric exclusivity incentive is working and successfully meeting the unmet medical needs in children.

In less than 10 years, the program has resulted in studies on about 120 diseases and conditions and has led to new labeling on about 120 new or already approved drugs for use in children.[10] The recent GAO study found that almost all of the drugs (87 percent) that had been granted pediatric exclusivity under the BPCA have had important labeling changes as a result of pediatric drug studies conducted under BPCA.[11] According to GAO, the labeling of drugs was often changed because the pediatric drug studies revealed that children may have been exposed to ineffective drugs, ineffective dosing, overdosing, or previously unknown side effects.[12] The Elizabeth Glaser Pediatric AIDS Foundation has stated, "the [pediatric exclusivity] incentives are proven to deliver life-saving information for children—the same information that we expect and demand for ourselves as adults."[13]

Legislation Acknowledges Inherent Difficulties in Conducting Pediatric Studies

The legislation also has been a success because it addressed one of the fundamental impediments that in the past hampered the conduct of pediatric studies—the small number of pediatric patients. Fortunately, most children are healthy. In the adult population, there are larger numbers of patients who suffer from diseases like heart disease and diabetes and are available for clinical trials. In contrast, with pediatric patients, serious and chronic illness is caused by a wide range of diseases, but for the most part there are few children affected by any particular disease. For example, fewer than 0.5 percent of patients with arthritis are children, and juvenile rheumatoid arthritis is a different disease than adult rheumatoid arthritis and osteoarthritis.

This limited pediatric patient population has several consequences—first, clinical trials are more difficult to conduct with children. The trials are smaller because there are fewer children with a given condition. The children are also of different ages. As a result, they may need different, age-appropriate formulations of medicines for accurate and safe administration. In addition, the pharmacokinetics of drugs (i.e., the rate at which they are absorbed) varies by age.

Coupled with these technical, scientific, ethical and medical issues, there are also unique regulatory requirements relating to the study of drugs in children. Sometimes, a development program for pediatric drugs must include the duplication of an entire clinical program for each of the pediatric age categories for which an indication is sought. So, for example, if the clinical development program included adults 16 years of age and older and the sponsor wishes to investigate safety and efficacy in children 12 to 16, tolerance studies may be required. These tests can be

[7] "FDA Joins Children's Health Groups to Mark Historic Milestone for Pediatric Drugs," FDA Press Release, December 19, 2005.

[8] Jennifer Li, op cit.

[9] "Pediatric Drug Research: Studies Conducted under Best Pharmaceuticals for Children Act," GAO–07–557 (March 2007).

[10] Pediatric Study Costs Increased 8-Fold Since 2000 as Complexity Level Grew, Impact Report, Tufts Center for the Study of Drug Development, Vol. 9, No. 2, March/April 2007.

[11] Pediatric Drug Research: Studies Conducted under Best Pharmaceuticals for Children Act, GAO–07–557 (March 2007).

[12] Id.

[13] "FDA Joins Children's Health Groups to Mark Historic Milestone for Pediatric Drugs," FDA Press Release, December 19, 2005.

followed by bioavailability and finally safety and efficacy in children with the disease. If the sponsor then chooses to seek the indication in children ages 6 to 12, the initial studies would again be tolerance studies followed by bioavailability studies before the safety and efficacy studies could begin. This process could continue for the age groups below 6 years of age, i.e., 3 to 6, 1 to 3, 6 months to 1 year and less than 6 months.

It is clear that a clinical development program necessary to address all age groups for children can be more extensive than a development program needed to address the age group 16 to 65. And, once formulations are produced and validated, studies are performed, regulatory hurdles are met, and labeling is ultimately changed, the market for most medications for children is very limited. The enactment of the pediatric exclusivity incentive in FDAMA and later reauthorized in BPCA have made these hurdles less daunting and more feasible for companies to overcome.

DESPITE RISING COSTS AND ADDED COMPLEXITIES, COMPANIES ARE STILL RESPONDING TO THE INCENTIVE

According to the Tufts Center for the Study of Drug Development (hereafter referred to as the Tufts Center), the cost, length, and complexity of pediatric studies have expanded significantly since 2000. Despite that trend, companies are still investing and engaging in this important research and responding to FDA written requests at very high numbers. The GAO found that most of the on-patent drugs for which FDA requested pediatric studies under BPCA were being studied.[14] This conclusion is supported by the Tufts Center, which found an 84 percent industry response rate to FDA written requests for pediatric studies.[15] This exceeds the 80 percent response rate expected in FDA's 2001 Status Report to Congress.

Scope, Time and Costs of Pediatric Studies Expanded Significantly in Recent Years

From 2000 to 2006, the scope of pediatric studies has expanded significantly. For example, the average number of patients per written request increased 178 percent between 2000 and 2006, while the average number of studies per written request rose 60 percent.[16] There was also a doubling of the share of programs required to perform long-term follow-up studies (from 17 percent in 2000 to 33 percent in 2006) during this same time period.[17]

Additionally, the time required to complete pediatric studies nearly doubled between 2000 and 2006. Several factors contributed to the lengthening of study times, including increased complexity and scope of studies, as well as the availability of patients, investigators, and facilities, access to FDA staff, to name a few.[18] In addition to time, the average cost to respond to a written request increased 8-fold from 2000 to 2006. Total average out-of-pocket costs to complete a written request went from $3.93 million in 2000 to $30.82 million in 2006 (nominal dollars).[19] While these increases may have led some to speculate that the number of pediatric studies would decrease overall, the evidence clearly shows that this has not been the case.

Number of Efficacy and Safety Studies Grew by 60 Percent From 2000 to 2006; Most Studied New Drugs in Development and New Indications

The cumulative number of pediatric studies completed since 1998 rose from 58 at the end of 2000 to 568 at the end of 2006. Sponsors increased the proportion of efficacy and safety studies—the most expensive and time-consuming studies—from 25 percent in 2000 to 40 percent in 2006. Sponsors are continuing to break new ground—for example, 20 percent of written requests were for new drugs in development, 40 percent were for unapproved indications, while just 40 percent were for already approved indications.[20] Thus, even in the face of rising costs and increasing scope and complexity of pediatric studies, sponsors continue to respond.

THE PEDIATRIC EXCLUSIVITY INCENTIVE SHOULD REMAIN INTACT

The pediatric exclusivity incentive has had a tremendous positive impact on the lives of children. The current program is working well and its basic features should

[14] Pediatric Drug Research: Studies Conducted under Best Pharmaceuticals for Children Act, GAO–07–557 (March 2007).

[15] Pediatric Study Costs Increased 8-Fold Since 2000 as Complexity Level Grew, Impact Report, Tufts Center for the Study of Drug Development, Vol. 9, No. 2, March/April 2007.

[16] Id.

[17] Id.

[18] Id.

[19] Id.

[20] Id.

not be altered. Changes in the current program could reduce the incentive to conduct pediatric studies.

Exclusivity is Not a Guarantee

It is important to remember that despite the incentive the pediatric exclusivity program has provided, pediatric studies are done at risk. As a preliminary matter, the FDA may determine that a company's studies do not fairly respond to the written request and therefore the company would be denied exclusivity. Further, programs may fail due to technical reasons, lack of sufficient patients, problems with study design, inadequate time to complete studies prior to loss of exclusivity, etc. In fact, according to the Tufts Center, about half of submitted pediatric studies led to an award of pediatric exclusivity; the rest were rejected or were still awaiting an FDA decision by the end of 2006.[21]

In addition, even when a company is granted exclusivity, the value of such exclusivity may be diminished (or nullified) due to other factors. For example, a successful Paragraph IV patent challenge by a generic competitor may nullify any pediatric exclusivity award. In this instance, a company does not benefit from the grant of pediatric exclusivity for the product at issue. Approval of new products in the same class may reduce market share for a product as well, thereby diminishing the value of any pediatric exclusivity. These scenarios are not easily predictable, particularly at the early stage of drug development in which pediatric studies must be contemplated. So, even in the instance where a company is granted pediatric exclusivity, there is not a guarantee of what the value of that incentive may be down the road due to potential early generic entry or diminished market share as a result of increased class competition.

Majority of Medicines Studied by Sponsors Were Not in the Top 200 Sellers; Blockbuster Drugs Receiving Pediatric Exclusivity Have Helped to Build the Necessary Infrastructure for Sustainability and Continued Growth of Pediatric Programs

Pharmaceutical companies have pursued pediatric studies for many products that are not top-selling medicines. In fact, less than half of the products that received pediatric exclusivity were in the top 200 selling drugs, according to the Tufts Center.[22] Some of these include medicines for HIV/AIDS, leukemia, anti-infectives, antihistamines and anesthetic drugs. In addition, only about one-tenth of drugs awarded pediatric exclusivity were in the "blockbuster" category.[23]

While blockbuster drugs represent only one-tenth of the drugs awarded pediatric exclusivity, the exclusivity benefits of one blockbuster drug can support pediatric studies for other drugs and can support and expand infrastructure for pediatric drug programs. As with drug development in general, higher revenue drugs support the ability of pharmaceutical companies to invest in research for medicines with lower expected revenue. In the case of pediatrics, not only have blockbuster drugs allowed companies to invest in research for lower revenue products, they have also given companies the ability to build pediatric programs and infrastructure over the past decade. Prior to enactment of the pediatric exclusivity incentive, such infrastructure did not exist.

According to Dr. Floyd Sallee, M.D., Ph.D., a child psychiatrist and director of the pediatric pharmacology research unit at Cincinnati Children's Hospital Medical Center, "There was no infrastructure for the research before . . . Drug companies have hired pediatric experts and there is a larger network of expertise to draw from."[24] Dr. Sallee's comments were echoed by an industry expert, Dr. Stephen Spielberg, M.D., Ph.D., "The legislation has encouraged the development of needed infrastructure, highly specialized staffing needed to develop pediatric formulations and to perform pediatric clinical studies."[25] Similarly, the GAO has testified that, "Experts agree that, since FDAMA, there also has been significant growth in the infrastructure necessary to conduct pediatric studies . . . The pharmaceutical industry has also increased its capacity to conduct pediatric studies since enactment of FDAMA."[26]

Revenues from top-selling products can support pediatric and adult drug research and development in other "non-blockbuster" areas. "Since research resources are al-

[21] Id.

[22] U.S. Pediatric Studies Incentive Led to New Labeling for Nearly 100 Drugs, Impact Report, Tufts Center for the Study of Drug Development, Vol. 7, No. 4, July/August 2005.

[23] Id.

[24] "Drug Research and Children," FDA Consumer (January—February 2003), *http://www.fda.gov/fdac/features/2003/103 drugs*_html.

[25] Testimony of Stephen P. Spielberg, M.D., Ph.D., before the Senate Committee on Health, Education, Labor, and Pensions, Hearing on Pediatric Drug Development, May 8, 2001.

[26] S. Rep. No. 107–79 (October 4, 2001).

located across drug portfolios . . . these medicines indeed provide the fuel to drive research and development of less remunerative compounds . . ."[27] Dr. Spielberg continued, "For currently marketed drugs, establishing and maintaining excellent pediatric drug development programs can be driven to some extent by higher income medicines."[28]

Congress has also recognized the relationship between the incentive and development of pediatric research infrastructure. "The [Senate HELP] Committee is aware that the incentives created by the pediatric exclusivity provision have encouraged the drug industry to develop and expand its infrastructure and expertise in the study of drugs in pediatrics."[29]

The pediatric exclusivity incentive must be preserved to ensure that pediatric drug development is not hindered in the face of uncertainty over likelihood of reauthorization and rising research costs. Diminishing or otherwise reducing the value of the incentive could also create unintended ripple effects across the entire program. While some have argued the return some products (namely blockbuster drugs) have received as a result of pediatric exclusivity are not in line with the cost of the studies undertaken, the fact is that blockbuster drugs have created the ability for companies to invest in pediatric programs and infrastructure necessary to conduct research across a company's portfolio. Taking away or reducing the incentive for blockbusters could have unintended consequences across the program.

Regardless of other aspects of health economics and health-care financing, the small number of pediatric patients with a specific disease available for study, the rising costs and added complexity of the studies, and the ultimate limited market for pediatric drugs will remain. That is why it is important to maintain the robust public policy that to date has so successfully promoted research on children's needs.

CONCLUSION

PhRMA strongly urges Congress to reauthorize the BPCA. The increasing rate of industry study proposals and written requests for studies by FDA shows continuing progress, which would be significantly undermined if this important legislation were allowed to expire. In addition, we urge Congress to proceed with caution when considering changes to the incentive that could have unintended consequences to pediatric research.

PREPARED STATEMENT OF THE SOCIETY FOR CARDIOVASCULAR ANGIOGRAPHY AND INTERVENTIONS

The Society for Cardiovascular Angiography and Interventions supports the Pediatric Medical Device Safety Act of 2007. We greatly appreciate this effort to expand pediatric patients' access to safe medical devices. This proposal will be an important step forward.

The Society for Cardiovascular Angiography and Interventions (SCAI) is a professional association representing over 3,700 invasive and interventional cardiologists. SCAI promotes excellence in cardiac catheterization, angiography, and interventional cardiology through physician education and representation, and quality initiatives to enhance patient care.

Fortunately, cardiovascular disease is far less common in the pediatric population than it is in the adult population. This good fortune does however frequently lead to unique challenges for the pediatric interventional cardiologist who treats these patients. Some of the challenges are clinical and we are more frequently solving those problems, saving children's lives and avoiding the trauma of surgery. Other challenges, and perhaps the most frustrating ones are related to obtaining the safe medical devices necessary to treat these patients. Devices that are available to our colleagues in Europe are not available in America. We support the FDA's efforts to ensure that only safe and effective medical devices are used on patients in our country, but when the entry barriers into the American markets are so high that manufacturers refuse to enter—some patients suffer and die needlessly. Required is an appropriate balance between the sometimes mutually exclusive goals of safety and availability.

We are especially pleased that your legislation will require the FDA to issue guidance to institutional review committees (IRCs) on how to appropriately consider the use of the humanitarian device exemption (HDE) at their institution. When HDE devices are not part of an ongoing trial, IRC's (which focus on reviewing the care of patients in trials) are sometimes confused.

[27] Id.
[28] Id.
[29] S. Rep. No. 107–79, October 4, 2001.

We believe that giving the FDA explicit statutory authority to extrapolate from adult to pediatric patients in appropriate situations could help FDA officials expedite their review of some pediatric medical devices.

We applaud the provision that allows companies to make a profit on HDE devices designed for children. This change will encourage the development of more devices by providing an opportunity for profit and also by reducing concerns about audits, specifically those using different assumptions which could determine a profit was made when a manufacturer calculated their financial situation differently. We note that the 4,000 cap is arbitrary and far below the limit that is placed on orphan drugs. We believe that more devices could be made available to pediatric patients and those with congenital heart disease if that cap is raised. We encourage you to consider such an increase either as a part of this legislation or broader FDA reform legislation.

We also understand that there are some concerns on the part of industry about the section 522 provisions of this proposal. As clinicians, we are not in a position to evaluate the precise impact of those provisions but we certainly hope those concerns can be resolved.

We look forward to working with you and your staff to support passage of this legislation and thank you once again for your efforts. SCAI's contact person regarding this legislation is Wayne Powell and he may be reached at (202) 375-6341 or *wpowell@scai.org*.

AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS (AAOS),
WASHINGTON, DC. 20002–5701,
March 22, 2007.

Hon. EDWARD M. KENNEDY,
Chairman,
Committee on Health, Education, Labor, & Pensions,
Senate Dirksen Office Building,
Washington, DC 20510.

DEAR CHAIRMAN KENNEDY: The American Association of Orthopaedic Surgeons (AAOS) representing 17,000 board-certified orthopaedists thanks you for your continued commitment to pediatric issues. As one of the founding members of the Orthopaedic Device Forum comprised of liaisons from the Centers for Medicare and Medicaid Services, the Food and Drug Administration (FDA), the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Biomedical Imaging and Bioengineering, the Orthopaedic Research Society, the Orthopaedic Surgical Manufacturers Association, the American Society for Testing and Materials, and the American Orthopaedic Association, the AAOS has a long history of working directly with the FDA on concerns of advancing orthopaedic patient care.

As stakeholders with significant use of medical devices, AAOS fellows treat many pediatric patients. Our association is committed to advocating for regulatory policies that provide for optimal patient-centered care while adhering to the least burdensome provisions of the Food and Drug Administration Modernization Act (FDAMA).

The AAOS appreciates your committee's willingness to work with all stakeholders on the Pediatric Medical Device Safety and Improvement Act of 2007 (S. 830). Bringing small volume products to the U.S. market is a complex problem with important nuances. Therefore, we are concerned that some of the provisions, if enacted into law, will have unintended consequences of discouraging the development of pediatric devices. Our letter will highlight some concerns with provisions in the legislation including postmarket surveillance, post-market surveillance investigations, humanitarian device exemptions, clinical trials database, and the proposed consortium.

POSTMARKET SURVEILLANCE

The AAOS believes that a lengthy post-market surveillance mandate will hinder pediatric device development as there is no ceiling attached to the language. The FDA has sufficient authority in Sec. 522 of the Federal Food, Drug, and Cosmetic Act to extend postmarket surveillance beyond 36 months and has negotiated 10-year postmarketing studies with the manufacturers of two of the last successful orthopaedic pre-market approvals. Several large manufacturers communicated their aversion to developing and producing devices with a long post-market surveillance review, particularly with small volume products, as they cannot recoup their development costs.

POST-MARKET SURVEILLANCE INVESTIGATIONS

Moreover, expertise on post-market surveillance event investigations resides within the Centers for Devices and Radiological Health. While the Office of Pediatric Therapeutics may serve as a coordinating center, they do not possess the experience to evaluate device adverse events. The AAOS suggests that this language be amended to reflect the appropriate Federal authorities assigned to investigate adverse events.

HUMANITARIAN DEVICE EXEMPTIONS (HDE)

While the AAOS does not take a position on manufacturers' ability to capture a profit on HDE devices, the AAOS contends that a lengthy Institutional Review Board (IRB) process is a deterrent to at least two of the current manufacturers of pediatric HDEs in the U.S. market. Delays of up to 5 years were reported to the AAOS due to misunderstandings of the IRBs reviewing a marketed product rather than original research. Since the FDA issued a guidance document in January 2006 on this topic, communication between the IRBs and the FDA about the contents of this guidance may facilitate more expeditious IRB reviews.

In any case, humanitarian devices are generally sold in the tens or hundreds; as such, profit potential is limited. If profit potential is to be allowed on HDE devices, AAOS recommends the application of the same policy for all currently marketed humanitarian devices regardless of whether the indications are for use in pediatrics, adults, or those devices with general labeling. This policy will help ensure that the currently marketed HDEs remain on the U.S. market.

Determining the number of humanitarian devices for an appropriate indication and then subsequently capping the number at 4,000, seems to be a sub-optimal use of resources. The AAOS suggests maintaining the cap of 4,000 and deleting any provisions to determine an annual distribution when submitting a humanitarian use device designation.

CLINICAL TRIALS DATABASE

As you are aware, the FDA has very limited funding and as such, the AAOS finds the new clinical trials database to include information on Sec. 522 devices very resource intensive. This database is also duplicative of some post-market surveillance efforts currently underway at the FDA. To have useful public utility, databases should answer important research questions. This database does not appear to be linked to the adverse event databases at the FDA; therefore it appears to serve more of a public educational function, rather than a clinical outcomes function.

CONSORTIUM

The AAOS appreciates that $6 million per annum will be devoted to pediatric device development through the consortium for fiscal years 2008–2012. Substantial outcomes must be delivered and parties must be held accountable for considerable progress in the development of pediatric devices.

REGULATORY VS. LEGISLATIVE SOLUTIONS

Our experience has affirmed that many problems can be solved with a change in regulatory interpretation or alterations to FDA regulatory policy. After 11 years, the Orthopaedic Device Forum accomplishments include device reclassifications, guidance document development, and defining a regulatory pathway for a previously unmarketed product all without legislative interventions.

The AAOS supports significantly increased appropriations for the FDA to carry out the important mission of protecting and promoting the public's health. Furthermore, with our years of experience in working with the FDA, we hope that your office will consider the AAOS as a resource for FDA issues. We look forward to working with you.

Sincerely,

JAMES H. BEATY, M.D.,
AAOS President.

[Whereupon, at 2:40 p.m., the hearing was adjourned.]

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