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PROGRAMS AFFECTING SAFETY AND INNOVATION IN PEDIATRIC THERAPIES

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE
HOUSE OF REPRESENTATIVES

ONE HUNDRED TENTH CONGRESS

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PROGRAMS AFFECTING SAFETY AND INNOVATION IN PEDIATRIC THERAPIES

TUESDAY, MAY 22, 2007

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 10:15 a.m., in room 2322 of the Rayburn House Office Building, Hon. Frank Pallone, Jr. (chairman) presiding.

Members present: Representatives Waxman, Eshoo, Green, Capps, Allen, Schakowsky, Hooley, Matheson, Deal, Murphy, Burgess, and Blackburn.

Also present: Representative Markey.

Staff present: Ryan Long, Nanden Kenkeremath, Chad Grant, John Ford, Bobby Clark, Jack Maniko, Virgil Miller, and Melissa Sidman.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. We have no amplification, so we urge everyone to speak loudly. There is no point speaking into the mic or turning it on. It is not working. We will have no Web cast, so for those who want to watch us from a distance, they are out of luck. We also have no transcript. I apologize, we are going to have a transcript. We are going to do the best we can. Thank you. It may not be a full transcript because we may not be able to hear everything; but yes, there will be a transcript, it just may not be complete. Other than that, we are following normal procedures. And the air-conditioning works, too, just so you know. So I will recognize myself for an opening statement initially.

Today the subcommittee is meeting to hear about programs affecting safety and innovation in pediatric therapies. Today's hearing is of critical importance because above all else, we must ensure that the prescription medications and devices our children use are in fact tested appropriately and deemed safe. I believe that we all agree, regardless of our party affiliation, that we have an enormous responsibility to our children to ensure that they have access to the best possible medical treatment. And today we will hear about two existing programs designed to facilitate better testing of drugs in children. They are the Best Pharmaceuticals for Children and the Pediatric Research Equity Act. Combined, these two programs are often referred to a carrot-and-stick approach used by the FDA to

encourage and direct drug manufacturers to test their products for pediatric use. We will also discuss the need to encourage better research and development of medical devices for pediatric populations. Under BPCA, in exchange for completing a pediatric study requested by the FDA, a drug manufacturer can receive a 6-month extension of market exclusivity for the product that is studied. This model has proven successful in providing new and valuable information about the appropriate pediatric use of many drugs. According to the GAO, who we will also hear from today, drug manufacturers agree to the pediatric studies requested by FDA for on-patent drugs 81 percent of the time. These studies have resulted in important labeling changes that help providers and parents determine the best course of treatment for a child stricken by a particular illness or chronic condition.

In the past, I have raised concerns about the financial impact an additional 6 months of market exclusivity has on American consumers. While the incentive under BPCA is clearly working to encourage companies to conduct the studies that FDA requests, at the same time this type of patent extension serves as an obstacle that blocks access to generic drugs for consumers, forcing them to pay higher prices because lower-cost alternatives are kept off the market.

In looking over how the program has worked over the past 5 years, I am concerned about the amount of earnings drug manufacturers receive in exchange for completing these studies. The financial gain the drug makers receive from the market exclusivity under BPCA usually far exceeds the costs incurred in completing the pediatric trials requested by FDA. There may be a better way to balance the need to provide incentives for drug manufacturers who conduct pediatric studies and ensuring consumers have timely access to lower-cost prescription drugs.

The Pharmaceutical and Research and Equity Act, or PREA, is the other component of this approach, and gives FDA the regulatory authority to require certain pediatric assessments for a particular drug in which a drug maker is submitting an application. The regulatory authority granted to FDA under PREA is linked to the expiration of BPCA and thus will also expire at the end of this fiscal year. This makes very little sense to me. Why should we put a timetable on providing the FDA with the regulatory power to ensure drug companies conduct research necessary to ensure that our children have access to safe and effective medicines? We don't place such limits on FDA when it comes to conducting research on adult populations, and so we shouldn't do it for our children, either.

Aside from drugs, we also have a responsibility to ensure that children have access to appropriate medical devices. You know that we had a hearing on PDUFA last week, but today we also want to look at the children's aspect. The problems that we face in encouraging pediatric studies of drugs are parallel to the problems that we face in encouraging similar research in the device world. There are few medical devices designed to be used in kids. Instead, doctors are often forced to jury-rig devices that are designed to treat adults. We need legislation that will encourage device manufacturers to do their research and development necessary to provide our children with devices that will fit their small and growing bodies.

Again, I can't emphasize enough that testing of drugs and devices for pediatric use is essential. As a father of three young children, I know how critical it is that we ensure our children with access to the treatments and therapies they need to live happy and healthy childhoods. I also want to say that I know how important these issues are to members of this subcommittee on both sides of the aisle. Ms. Eshoo, Mr. Waxman are the voices in the debate about encouraging pediatric studies for prescription drugs. Mr. Markey and Mr. Rogers have been strong advocates on the need for medical devices to be made available for kids, and I am going to work with all of you to ensure that we pass legislation that includes access to the medical treatment our Nation's children need.

Again, I want to thank all of our witnesses for being here today even though we are dealing with certain limitations here in terms of the technology, and we are the technology committee. So I don't really know what to tell you.

I will yield to our ranking member for 5 minutes. Thank you.

OPENING STATEMENT OF HON. NATHAN DEAL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF GEORGIA

Mr. DEAL. We are going to have to stop letting the Telecommunications Subcommittee use this room. Meeting medical needs of children in the innovative world of today's medications and medical devices presents a challenge because of their smaller share of the market and the typical focus on adults in the testing of any new product. The Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act were important steps toward promoting research in pediatric education or medical therapies. I know our witnesses will highlight that the effect of a medication on a child is not necessarily the same as an adult, and further study is necessary to establish the safety and effectiveness of products for children.

Developing medical devices for use by children also creates a unique challenge. As we evaluate the reauthorization of our current programs which focus on pediatric testing, I look forward to the testimony of the witnesses about their successes but also ways to improve these programs. I would also like to hear about what should be done in other areas of pediatric devices.

I thank our witnesses for their attendance today, and I look forward to your testimony. I yield back my time.

Mr. PALLONE. Thank you. Mr. Waxman.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you very much, Mr. Chairman. When a pharmaceutical company gets a drug approved, for the longest period of time they never bothered to check what the dosage would be for children. And that frustrated parents and pediatricians because they didn't have that information. So originally we decided to give an incentive for that test by giving the pharmaceutical company an additional 6 months of exclusivity over their drug. Then Congress passed another law saying, well, at least when they come in for their first approval, we ought to require them to do the tests

for children, and that should be a condition for approval. So we had both laws working now to make sure that we get the pediatric tests.

The first law that requires that they test the drugs on children before approval of the drug at all has been sunsetted, and we ought to remove that sunset. It ought to be a permanent feature of our law.

The second one which gives the exclusivity as a reward for these tests should be extended, but I think we need to think through a number of different issues. One, in many cases, 6 months is too generous a reward. It, in some cases, over 100 times rewards the company for the expenditure of money to do the test. And it is all at the expense of consumers because the consumers have to wait an additional 6 months after continuing to pay the high monopoly price for the drug. I think that we need to evaluate how generous we should be in rewarding the drug companies for doing something that quite frankly they should be doing anyway. We also ought to evaluate the way that FDA acts in providing this 6-month or any type of exclusivity. The FDA has a very short period of time in which to make a decision, and we ought to give them enough time to decide whether the company has done work that merits a reward of exclusivity.

Some of the tests that the companies have done to gain this exclusivity really aren't all that targeted. They will do tests on a big-selling drug that really don't have the applicability for children, for example, doing tests on an anti-depressant that might never be used for children but by doing the test, they get a longer period of time for that particular drug which may be a very big-selling drug.

So I think we need to calibrate the reward for the job that we want done. We all want the tests to be accomplished for pediatric doses of these drugs. We need now at this time of reauthorization of the legislation to figure out the best way to accomplish those goals without putting the consumers at an economic disadvantage.

Mr. PALLONE. Thank you, Mr. Waxman. Mr. Burgess.

OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. BURGESS. Thank you, Mr. Chairman, and to Ranking Member Deal for holding this hearing. As we talk about the reauthorization of PDUFA, we come to some significant issues relating to their reauthorization with regard to the needs children. When it comes to children, drugs can react differently than they might in adults; and medical devices need to fit on their bodies that are still growing and bodies that are active in ways that many of us could no longer remember.

My old professor of pediatric surgery, Dr. Vangy Brooks down in Houston, perhaps the patron saint of pediatric surgery, summed it up best one morning to a group of us medical students when she looked at us and said, you know what, kids are different. And indeed they are. I think we will hear that from several of our witnesses this morning that children are more than just little adults. They react differently to devices and drugs, and our Federal regulations should be crafted in a way that is sensitive and provides appropriate safeguards to protect their health and ensure their safety

for their unique situation where an implant may be placed into a growing body and is active in ways that we can only vaguely remember.

At the same time, overregulation can have a negative effect in the impact on the development and availability of drugs and devices for children, especially in the medical device realm in a pediatric environment where patient population can be small, both in number and literally, companies have huge incentives to enter the market. I believe that we need to expand on incentives that are currently available under the law such as the Humanitarian Device Exemption to encourage more companies to conduct research and more development in this important field.

Now, we are going to be hearing from several witnesses this morning, and I am especially glad to be hearing from Mr. Rozynski from the Stryker Corporation. They have a big presence in my district down in Flower Mound, TX, but what really excites me is some of the work in Dr. Rozynski's testimony that Stryker has done absolutely changing the landscape of the treatment of pediatric bone cancer, changing the environment for diseases as diverse as CLEP and cranial synostosis. The non-healthcare expenses related to moving a child or getting a child treated at the Center of Excellence are big, but Stryker has stepped up to the plate and said we will bear some of those expenses not covered by traditional insurance. These are particularly exciting events that are occurring, and I certainly salute Stryker and their corporate benevolence for looking and recognizing that this is important.

Additionally, we are going to hear from Dr. Gorman. His testimony will be illustrative of the clinical difficulties with treating children with outsized tools and medications that react differently in their bodies.

Over the past several years, I believe the drug and device industry, medicine, and its regulators have made important strides in improving safety and efficacy of pediatric drugs and devices. As this committee works on legislation relating to both, I hope this hearing will be instructive and our legislation will be appropriately inspired.

Thank you, Mr. Chairman. I will yield back.

Mr. PALLONE. Thank you. Ms. Eshoo.

OPENING STATEMENT OF HON. ANNA G. ESHOO, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Ms. ESHOO. Good morning, Mr. Chairman, and thank you for having this very important hearing. Despite our efforts, approximately 75 percent of drugs and a large majority of medical devices used by children have not been tested specifically for that use. So we have our work cut out for us. I think while the Congress has taken very, very important steps to turn these statistics around, understanding that children are not small adults. We recognized this fact in 1997 with the initial authorization of Best Pharmaceuticals for Children Act. I am very proud to be the Democratic sponsor of that, and again in 2003 with the enactment of Pediatric Research Equity Act. And together, I think that these two laws

have established what might be called a carrot-stick approach to pediatric drug testing that has been I think very successful.

Now, we are on the threshold of reauthorizing them, and as we reauthorize, we not only build on the successes of the past but I think having learned some things that we need to add some important things that will hopefully, when the next reauthorization comes around, that we can hail some more successes.

I think that the successes are evident because the laws have generated important, new information about safety and the efficacy of drugs prescribed to children. Pediatricians now know more about what therapies work and don't work in children. Unfortunately, nearly two-thirds of drugs currently used in children are still not labeled for their use. We need these two laws as I said renewed and improved if we want progress to be continued.

In the coming days, I am going to be introducing legislation to reauthorize both of these programs, and my legislation is going to make permanent the FDA's authority to require pediatric studies. This adjustment I think is consistent with FDA's permanent authority to require studies of adult formulations. I am also going to incorporate many of the recommendations of the GAO, the American Academy of Pediatrics, and the Elizabeth Glaser Pediatric AIDS Foundation; and I want to thank all of them, for all of these organizations for helping in the development of the legislation.

Medical and surgical devices designed just for children also need to be developed, but experience tells me that it won't happen without legislation. I think the Pediatric Medical Devices Safety Improvement Act is an important step in that direction. So I am confident that we are going to reauthorize, and I think passage of not only the reauthorizations but the Pediatric Medical Device legislation is going to protect children, really our Nation's most vulnerable citizens. They can't do these things for themselves.

I would also like to pay tribute to what Dr. Phil Pizzo, one time was at NIH. He is a pediatrician by background, and today heads up the Stanford Medical School; and he has been of great assistance to me, and I think without his steady, sure advice that we wouldn't have had the previous legislation and hopefully really sound legislation this time around.

Thank you, Mr. Chairman, and I look forward to working with all the committee members on this. These are not partisan issues by any stretch of the imagination. So I have confidence that we will be a solid group here, reauthorize and reform at the same time. Thank you. Thank you to our witnesses.

Mr. PALLONE. Thank you. The gentlewoman from Tennessee.

OPENING STATEMENT OF HON. MARSHA BLACKBURN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TENNESSEE

Mrs. BLACKBURN. Thank you, Mr. Chairman, and I do thank you and Ranking Member Deal for allowing us to engage in this discussion today with our witnesses, and we thank you for the time that you are giving to us for our hearing today. We know from so many different agencies and so many different participants that having this current pediatric exclusivity program has done quite a bit to spur some research and development and to generate some critical

information about the use of medicines in pediatric patients. And it is done more than probably any other Government initiative, and so we are interested in how to best go about and how to best approach the reauthorization of the Best Pharmaceuticals for Children Act. And it does give us a unique opportunity, I think, to expand our knowledge about the safety, the effectiveness of the products that are used with our children and to certainly protect our children as they are a part of our medical community.

Prior to passage of this legislation there was little incentive that existed to conduct clinical trails on pediatric use of medicines developed primarily for the adult population. The success of the BPCA has equipped doctors with accurate information about which drugs and which doses work best for our children. The pediatric exclusivity provision of the BPCA provides a critical incentive for our biopharmaceutical companies and for that research to invest in lifesaving drugs for our pediatric patients. This incentive has helped these companies, many companies of all sizes, to develop innovative medicines and protocols that would improve the lives of our children.

We are so fortunate in Tennessee to have some wonderful work that is being done at St. Jude's and also at Vanderbilt with our children; and we have talked with these researchers and we talked with some of these innovators and the scientists, and we know the importance of this legislation to their work. We know also it is important to keep our attention to preserving their right to the intellectual property and the research that they do. And we will continue to focus on that.

It is good legislation. As we move forward, I hope that our focus in our discussion will remain on how we preserve access to these protocols and therapies and formulations for our children.

Thank you, Mr. Chairman. I yield back.

Mr. PALLONE. Thank you. Our vice chairman, Mr. Green.

OPENING STATEMENT OF HON. GENE GREEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. GREEN. Thank you, Mr. Chairman, for holding this important hearing on pediatric therapies and our efforts to ensure their safety and continued development. Most of the prescription drugs we give children to cure their illnesses or treatment received are actually drugs that are developed for adults and prescribed off-label for children. While this is a common practice, it is clear that children are simply not little adults. By treating children with drugs that were developed for adults, we run the risk of exposing them to ineffective drugs. Even worse is off-label use of drugs could result in improper doses of drugs or adverse reaction for children that would not necessarily appear in adults. Currently 75 percent of drugs have not undergone studies in pediatric populations or even pediatric party populations. Any one drug is too small for a manufacturer to have the incentive to commit the resources or the testing. To provide that incentive, we enacted the Best Pharmaceuticals for Children Act which would provide an additional 6 months of market exclusivity for market products when their sponsor agreed to perform pediatric studies on the drug. In some respects it has been a success. In the drugs granted pediatric exclu-

sivity, 87 percent saw the changes to their label as a result of pediatric studies. These changes suggest that labels now provide physicians with better information, specific to the drugs indication for children. On the flip side, however, there are one out of five manufacturers that received FDA requests for pediatric studies that declined to conduct the studies; and today, none of these drugs have been studied for pediatric populations.

I look forward to hearing from our witnesses on how we can improve the Best Pharmaceuticals for Children Act and encourage even better prescriptions from drug sponsors. Any discussion of the Best Pharmaceuticals for Children Act should also be accompanied by the discussion of the Pediatric Research Equity Act which for all intents and purposes will expire at the end of this fiscal year along with the Best Pharmaceuticals for Children Act. In this statute, we give the Secretary the ability to require manufacturers to study drug safety and the effectiveness of children. If the manufacturer doesn't comply with the request, the Secretary can consider the product misbranded. However, the Secretary doesn't have any enforcement action short of—misbranded. I would like to learn what additional authority Congress can give the FDA to better align the research obligations and the appropriate enforcement effectiveness with the end result of better information on the safety and effectiveness of drugs involving our children. And again, like everyone else, I would like to thank our witnesses for being here today and thank you for what you do every day regarding the health of our children. I yield back.

Mr. PALLONE. Thank you. Mr. Murphy.

OPENING STATEMENT OF HON. TIM MURPHY, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. MURPHY. Thank you, Mr. Chairman. As we look at reauthorizing this bill, one of the things that I want to make sure that we are working on here has to do with the issue of being very careful that we are not taking away incentives in order to develop new drugs. Any reauthorization that limits the money a company can make and suddenly says you are making too much, we need to take that away from you, concerns me if it ends up reducing money that is used to develop new drugs. Let me give some examples.

When we look at a blockbuster drug that has emerged, we are looking at something that is the outcome of years of testing in which hundreds of millions of dollars may have been invested to that end, including funding many dead-ends along the way. There is also the issue about spin-off effects of profits that have funded the research of the past in other diseases as well and can be used for investments in researching other diseases in the future. But even when there is a blockbuster drug that emerges and one that may result in high profits, the risks do not end there. New problems may be found. For example, the news that came out about a drug called Avandia used to treat Type II diabetes, has had a big effect upon some of the profits and losses and stocks for GlaxoSmithKline. And although the outcome of that is being disputed, regardless of that, still it does have an effect upon the stock. It also has an effect then actually upon the profits and then the

subsequent effects upon things with regard to lawsuits. So any time we begin to look at such things such as profits, I hope we look at what are some of the long-term effects on how to review that.

Another area I want to make sure with this that we don't harm is the treatments and drugs that come for orphan diseases. There is an NIH office for rare diseases, and this helps us with advances in other areas so for those researching an area of a rare disease, it oftentimes helps us come up with treatments for other more common diseases that we didn't specifically know about in the first place. This is an area of such importance that in 1983 Congress passed the Orphan Drug Act to provide financial incentives for drug companies and biological manufacturers such as tax credits, Government grants, other research assistance, and 7-year exclusivity on development. Because these extremely rare diseases were ones that certainly didn't have the numbers to create profits big enough or the money even to invest in some of the research, these being infectious diseases, immune deficiency diseases, autoimmune diseases, analogies that could be exaggerated if the immune systems are compromised.

Many of these areas are ones that I want to make sure we continue with this funding stream. So I hope whatever road we go down is one we are very careful to make sure that funding is still there in the future to come up with some of the medications we need, particularly for rare childhood disorders, as we proceed forward.

Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. Mrs. Capps.

OPENING STATEMENT OF HON. LOIS CAPPS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mrs. CAPPS. Thank you, Mr. Chairman, and good morning to you and to our witnesses for appearing with us today on this very important topic, pediatric therapies. I think it is so fitting we are holding this hearing at the same time our Speaker, Nancy Pelosi, is holding a national summit on America's children. Unfortunately, we can't be in both places at the same time, but several of us were at the kickoff at 9 o'clock; and the first panel I think is also very appropriate, the panel under the topic "the Science of Early Childhood——

Mr. PALLONE. Wait a minute. Mrs. Capps, just hold on a second. I am sorry. Go ahead.

Mrs. CAPPS. Well, I will leave that—maybe that is the path where we should be. But this is more directly attuned to a topic of great importance to our committee, and if the Secretary had this second on children's health and I appreciate that and I think it is a good sign of things to come.

As I mentioned in a hearing we had last week on a different topic, I am very concerned by the fact that research tends to focus on adult males while leaving out women and children; and we know that there are biological and physiological differences that need to be taken into account to best meet the needs of all men, women, and children separately; and of course, when it comes to testing medications and devices on children, we have to confront many additional ethical issues and some economic issues for the

lack of testing on children for one. The lack of proper testing on children results in a lot of off-label prescribing and for a lack of access to potentially lifesaving treatment. As has been mentioned already, 75 percent of drugs have had no pediatric testing, yet we know many of them are being prescribed for children. This puts all of our children at risk.

So our task becomes answering the question of how do we ensure safety. We have taken several steps to move forward in our quest to incentivize both the development of drugs and biologics for use in children. We also need to ensure that clinical testing in children is carried out to the highest ethically accepted standard. And as we move forward to find ways to improve existing frameworks developed through the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, we need to put in place incentives for medical device manufacturers as well. And so I look forward to hearing today from our witnesses on the current status of pediatric development as well as testing and learning about areas that need improvement. This is a work in progress. And most importantly I believe we all need to be working to figure out how we can ensure that both the Government and biotechnology industry keep children in mind as we move forward in developing and improving new medications. Thank you. I yield back.

Mr. PALLONE. The gentleman from Utah.

Mr. Matheson. I will waive.

Mr. PALLONE. Ms. Hooley, the gentlewoman from Oregon.

Ms. HOOLEY. I guess it doesn't matter if I turn on the microphone?

Mr. PALLONE. It does not, although I should tell you we are trying to correct it, and we might have some luck. But right now, we are operating without.

OPENING STATEMENT OF HON. DARLENE HOOLEY, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OREGON

Ms. HOOLEY. Well, first of all, Mr. Chairman, thank you; and I want to thank the witnesses for being here today. Ensuring that drugs and medical devices used by our children are safe and effective is a moral imperative for Congress and the FDA. The Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act have enabled us to make significant strides toward improving the safety of drugs prescribed for children. For example, labeling changes have been made to 87 percent of the drugs that are used exclusively in pediatrics. That figure demonstrates a tremendous value in pediatric testing and the imperative for Congress to take additional steps to push for increased clinical testing of drugs prescribed for children. Because of the incentives provided under BPCA, labeling changes have resulted in more appropriate dosing for children and disclosure of previously unknown side-effects. PREA has ensured appropriate pediatric testing can be required for new drugs and BPCA has been successful in incentivizing studies for on-patent drugs. Drug companies have conducted pediatric studies under BPCA on over 80 percent of FDA requests for on-patent drugs. I love all these initials. They are so wonderful. However, even with our successes, significant work remains to increase the prevalence of pediatric testing. Only four or five of the 10 most

commonly prescribed drugs for children have ever undergone pediatric testing. To increase pediatric testing, the FDA's very limited success with getting off-patent drug sponsors to conduct pediatric studies deserves more careful consideration. The National Institutes of Health has not funded studies on more than half of the off-patent drugs on which drug sponsors have declined FDA-requested pediatric studies.

The FDA must also reduce the amount of time between completion of its scientific review and approval of necessary labeling changes. Over 15 percent of drugs that require labeling changes under BPCA took more than 1 year from completion of the review process to a review of those labeling changes. The average time is nearly 9 months. Delays in making labeling changes may mean that children continue to receive inappropriate doses or that doctors remain unaware of potential serious side-effects for children. I hope the FDA does better. I also hope the FDA and the committee will look into the 2005 Institutes of Medicine Report on Pediatric Medical Devices for Reform Recommendations. As a starting point, the Center for Devices and Radiological Health should follow the IOM recommendation to form a division with expertise on pediatric devices. I look forward to discussing more of the IOM's recommendation on pediatric devices with the panelists during my question time.

Finally, it is imperative that as we take steps to expand testing of drugs and devices in pediatric populations that we do not produce unintended consequences that discourage development of products for children.

Thank you, Mr. Chairman. I yield back my time.

Mr. PALLONE. Thank you. We are going to take just a brief break to see if we can test the equipment. It might be working again. OK. Sounds like we are in order so we can use the equipment again starting with Mr. Allen who is recognized for 5 minutes.

Mr. ALLEN. Mr. Chairman, I will waive my opening remarks and submit it for the record.

Mr. PALLONE. OK. I think that ends all the opening statements. Any other statements for the record will be accepted at this time.

[The prepared statements follow:]

Statement for Congressman Edolphus "Ed" Towns
May 22 Hearing, Subcommittee on Health
"Programs Affecting Safety and Innovation in Pediatric Therapies," Rayburn 2322

THANK YOU, MR. CHAIRMAN FOR HOLDING THIS CRITICAL HEARING ON PEDIATRIC DRUG THERAPIES. I AM CONCERNED THAT THE U.S. GENERAL ACCOUNTABILITY OFFICE HAS FOUND THAT OUR SYSTEM OF STUDYING AND LABELING PEDIATRIC DRUGS OFTEN DOES NOT WORK. ONLY ABOUT ONE-THIRD OF THE DRUGS PRESCRIBED FOR CHILDREN HAVE BEEN STUDIED AND LABELED FOR PEDIATRIC USE. THIS HAS PLACED CHILDREN AT RISK FOR EXPOSURE TO INCORRECT OR INEFFECTIVE TREATMENTS AND OTHER HARMFUL ACTIONS. THE BEST PHARMACEUTICALS FOR CHILDREN ACT WAS DEVELOPED ABOUT FIVE YEARS AGO TO ALLOW THE FDA TO GRANT DRUG SPONSORS PEDIATRIC EXCLUSIVITY FOR SIX MONTHS IN EXCHANGE FOR CONDUCTING AND REPORTING ON PEDIATRIC DRUG TESTS. I AM CONCERNED THAT WHILE DRUG SPONSORS AGREED TO CONDUCT OVER 80 PERCENT OF THE STUDIES ORDERED FOR ON PATENT DRUGS, ONLY 34 PERCENT OF THESE STUDIES HAVE BEEN CONDUCTED. THE CONCERN IS THAT THE FDA GRANTED PEDIATRIC EXCLUSIVITY BASED UPON DRUG COMPANIES ACCEPTING WRITTEN REQUESTS.

THE OTHER CONCERN IS THAT FEW OFF PATENT DRUGS HAVE BEEN STUDIED UNDER THE 2002 ACT. WHILE WE ARE SPEAKING OF PEDIATRIC STUDIES, I AM ALSO CONCERNED THAT THESE STUDIES ALSO HAVE NOT INCLUDED A MORE DIVERSE SAMPLING OF CHILDREN WHEN APPROPRIATE.

MR. CHAIRMAN, WHILE I GENERALLY SUPPORT THE IDEA OF GRANTING A REASONABLE PERIOD OF EXCLUSIVITY WHERE DRUG SPONSORS AGREE TO CONDUCT ADDITIONAL DRUG STUDIES, WE MUST ADDRESS THE FACT THAT OVER SIXTY-FIVE PERCENT OF PEDIATRIC DRUGS HAVE NOT BEEN ADEQUATELY TESTED AND LABELED PLACING CHILDREN AT RISK FOR WRONG TREATMENTS AND WE MUST CORRECT THIS. MR. CHAIRMAN, I YIELD BACK THE BALANCE OF MY TIME.

PREPARED STATEMENT OF HON. HILDA L. SOLIS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. Chairman, thank you for holding this hearing today to discuss safety and innovation in pediatric therapies. Children are sometimes forgotten and left out because some consider them a small, niche market.

While the FDA's mission is to protect and advance the public's health, we must not forget that this must include children as well as adults. The FDA is also responsible for providing accurate, evidence-based information to the public so that individuals can make optimal health decisions. It is important to discuss and determine how we can increase the number and types of safe and effective medical devices and drugs designed for children. In order to do so, we must have accurate, scientific data on the safety and effectiveness of drugs and devices for children.

Before the enactment of the Pediatric Research Equity Act, 75 percent of the prescriptions that pediatricians wrote were for medications that had been found appropriate only for adults, even though their labels provided suggested children's dosages. As we know now, just because a drug has been proven safe and effective for an adult does not mean that it is equally safe and effective in a child. We must adjust medications and devices for children's small and rapidly growing bodies based on science, not guesswork. Improper medical treatments such as overdosing and underdosing can both lead to adverse health consequences. This is why medicines that will be used by children should be found safe for children.

Just as there are difference between children and adults, there are also differences among children of color. For example, the incidence of diabetes disproportionately affects Latino and Black children. We should maximize the effectiveness of drugs for the entire population. This means that when determining effectiveness and safety, we must ensure that the process includes the diverse group of children who represent the racial and ethnic groups that will likely receive the drug. I hope that FDA can now efficiently identify the participation rates of children of color under the pediatric exclusivity provision and that drug sponsors are required to use standard definitions for race and ethnicity.

Accurate data collection is essential in determining how children from different racial and ethnic react to specific drugs. We must enable providers and families to make the best possible decision about using medicines to improve their health.

I hope we can work together in a timely manner to ensure that our children have improved access to life-saving drugs and devices.

PREPARED STATEMENT OF HON. BARBARA CUBIN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF WYOMING

As the mother of two boys, I have made my fair share of trips to the doctor's office, not to mention the occasional emergency room visit. No parent wants to find out that their child is sick. But when it does happen, you hope that your physician has the knowledge and resources necessary to treat the problem.

In modern medical practice, pharmaceutical drugs have played an increased role in preventing, treating and curing disease. Yet federal drug safety policy fell behind in labeling these products for pediatric use. As few as 10 years ago, roughly 80 percent of medication labels in the Physician's Desk Reference were not labeled for children.

Biologically, children are not simply miniature adults. Off-label drug prescribing can result in a child receiving too much of a drug, or not enough for it to be effective. There can also be side effects unique to children, including effects on growth and development.

In 1997, Congress recognized this problem and granted a 6-month market exclusivity period to drug manufacturers who conduct the pediatric studies necessary for pediatric labeling. In 2002, this incentive was reauthorized in the Best Pharmaceutical for Children Act, or BPCA.

BPCA is arguably the most successful pediatric initiative the FDA has embarked upon. In conjunction with the FDA authorities granted in the Pediatric Research Equity Act, or PREA, the FDA has successfully spurred industry participation in the riskier pediatric labeling arena.

Because of this robust carrot and stick approach, I am please to report that my two grandchildren will have more access to pediatric specific labeling than I or their parents ever did. Today there is a pediatric study infrastructure that before was nonexistent.

I am confident that much of today's testimony will reaffirm the success of this approach. In reauthorizing BPCA and PREA, this committee ought to recognize the

important role of both voluntary market incentives and the FDA's authority to impose mandated studies in certain circumstances.

We still have a long way to go in fitting our treatments for pediatric settings. Nearly two-thirds of drugs used on children are still not labeled for children. We can, and should, do better than this. I am hopeful our panelists here today can share their suggestions for how Congress can best support our pediatric study infrastructure.

Let me turn to our first panel today.

First of all, welcome to all of you. Let me introduce each of you. We have, beginning on my left, Dr. Joanne Less who is Acting Director of the Office of Combination Products for the U.S. Food and Drug Administration; and then we have Dr. Sandra Kweder, Deputy Director, Office of New Drugs, Center of Drug Evaluation and Research at the FDA; and then last is Dr. Donald Mattison who is Chief Obstetric and Pediatric Pharmacology Branch of the National Institute of Child Health and Human Development at the National Institute of Health. Thank you all for being here.

We start with 5-minute opening statements from each of you. Your statements become part of the hearing record, and each witness, each of you in the discretion of the committee, may submit additional brief or pertinent statements in writing afterwards if you like; and I will start with Admiral Kweder.

STATEMENT OF REAR ADMIRAL SANDRA L. KWEDER, M.D., DEPUTY DIRECTOR, OFFICE OF NEW DRUGS, CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION

Dr. KWEDER. Good morning, Mr. Chairman, and members of the committee. I am Rear Admiral Sandra Kweder. I am a physician and the Deputy Director of the Office of New Drugs in the Center for Drug Evaluation and Research of the FDA. Dr. Joanne Less, the Acting Director of the Office of Combination Products, is accompanying me. She is here to respond to questions that you might have regarding pediatric devices. I am here today to share with you the real success of the pediatric exclusivity provisions that you have authorized and the Pediatric Research Equity Act. There is no question that they have expanded access to important therapeutics for children and importantly promoted safety and innovation in drug development for children.

Before the enactment of the exclusivity incentive program that began in 1997, about 80 percent of medications in the Physician's Desk Reference, a big compendium, did not have any pediatric use information; and only about 20 to 30 percent of drugs approved by FDA were labeled for pediatric use. Most drugs used for children were considered to be used off-label; in other words, there was no data to establish the correct dose in children or to confirm their safety profile or if they even were effective in children, the pediatric population. In 1997 you provided marketing incentives to manufacturers who voluntarily conduct studies of drugs in children. This law provides 6 months of additional market exclusivity for a drug in return for conducting pediatric studies in response to a very specific written request issued by FDA. The incentive had become the most successful pediatric initiative that we at FDA have ever participated in.

In 2002, the pediatric exclusivity incentive was reauthorized as this BPCA, the Best Pharmaceuticals for Children Act. This statute added provision for safety evaluation of products once they had received exclusivity, public dissemination of study information, and additional mechanisms for the study of drugs in children. Shortly thereafter, Congress passed another important law to work in concert with BPCA, the Pediatric Research Equity Act. PREA provides FDA authority to require pediatric studies under certain conditions. Since 1997, the exclusivity program has generated labeling changes for 128 products. These labeling changes have significantly increased the information available to healthcare professionals to use in the treatment of pediatric patients. Eighty-three products have updated new information expanding the use of the product to a broader pediatric population and labeling. Twenty-five have had dosing adjustments, important for clinicians, put in labels for pediatrics, and 28 products had information added to labeling indicating that the products were found not to be safe or effective in children. Thirty-seven had newer enhanced pediatric safety information added to labeling. This exclusivity, or BPCA, process can be initiated in two ways. FDA can determine if there is a public health need for additional pediatric studies for a drug and issue a written request on our own. Alternatively, a sponsor can initiate the process by submitting a proposal for a written request to us. However, even if the sponsor issues such a proposal, we will not issue a written request unless we perceive there to be an important public health need for those studies to be conducted.

Under BPCA, two review processes occur in parallel once we have data. One is the exclusivity review to determine whether the studies that the company actually did fairly respond to the terms we set forth in the written request that would therefore qualify the product for exclusivity. There is a separate process, a scientific review, to determine whether the NDA or supplement should be approved. And those two processes occur on different timelines. The scientific review is subject, however, to the same intense scientific rigor and administrative terms and conditions that we provide to any application that comes before the agency, and as part of that, we will decide whether changes to a product label are warranted at that time. Importantly, FDA includes both positive information and negative information from study reports done on pediatric studies in labeling because both types of information inform practitioners.

BPCA did several other important things that really have taught us a lot about the study of drugs in children and monitoring the safety of drugs in general. First, it authorized us to establish a Pediatric Advisory Committee that also provides for post-marketing safety review on a regular schedule by that committee of information on adverse events for all pediatric products granted exclusivity. It also created our Office of Pediatric Therapeutics as part of the Office of the Commissioner. This office provides scientific expertise and important ethics advice as we work with companies to guide pediatric product development. In contrast to BPCA which provides this voluntary mechanism for attaining needed studies on approved or unapproved indications of a drug, PREA, Pediatric Research Equity Act requires pediatric assessment of certain products

but only for the indications that are approved in adults. It is an important distinction, only for the indications that the sponsor is seeking adult approval for. FDA can defer or waive those pediatric assessments under certain circumstances. In contrast to BPCA though, PREA applies not just to NDA's or drugs, PREA also applies to biological products and biologic license applications. There have been about 40 labeling changes involving pediatric studies that are linked specifically to PREA.

Despite the success of the statutes, there are unquestionably a large number of drug and biological products that remain inadequately studied for children. BPCA and PREA have acted in concert to provide important safety, efficacy, and dosing information on pediatrics. We at FDA want to build on these improvements with more studies to produce new labeling information that is a value to the children in this country as well as physicians taking care of them.

We welcome the opportunity to work with you to ensure that the benefits of the incentive program continue in conjunction with our need for our continued authority to mandate studies. We are just getting on a roll, and Dr. Less and I will be happy to answer any questions.

[The prepared statement of Dr. Kweder follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT OF

REAR ADMIRAL SANDRA LYNN KWEDER, M.D.

DEPUTY DIRECTOR, OFFICE OF NEW DRUGS

CENTER FOR DRUG EVALUATION AND RESEARCH

FOOD AND DRUG ADMINISTRATION

BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

UNITED STATES HOUSE OF REPRESENTATIVES

"Programs Affecting Safety and Innovation in Pediatric Therapies"

MAY 22, 2007

Release Only Upon Delivery

INTRODUCTION

Mr. Chairman and Members of the Committee, I am Rear Admiral Sandra Kweder, M.D., Deputy Director of the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency). I appreciate the opportunity to discuss FDA's role with respect to implementation of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). Congress enacted these initiatives to promote drug development for children because of the inadequacy of pediatric use information for the majority of drug products approved in the U.S. These two pieces of legislation are real success stories. As discussed below, there is no question that they have expanded access to important therapeutics for children, and promoted safety and innovation in drug development.

Although these statutes have resulted in significant improvements in the development of information on the use of therapeutics in children, there is still great need for additional studies. Because children may present with different symptoms and have different reactions to treatments, it is important to study products which have been used to address carefully diagnosed pediatric conditions. Pediatric patients are subject to many of the same diseases as adults, and are, by necessity, often treated with the same drugs and biological products as adults. Even with the advancements of the past 10 years, the majority of drugs still lack pediatric labeling information, and this absence of information can pose significant health risks for children. Inadequate dosing information may expose pediatric patients to overdosing or underdosing. Overdosing could increase the risk of adverse reactions that could be avoided with an appropriate pediatric dose; underdosing may lead to ineffective

treatment. The lack of pediatric specific safety information in product labeling also means caretakers and physicians are unable to monitor for and manage pediatric-specific adverse events. In situations where younger pediatric populations cannot take the adult formulation of a product, the failure to develop a pediatric formulation that can be used by young children (e.g., a liquid or chewable tablet) also can deny children access to important medications.

BACKGROUND: BPCA and PREA

Before enactment of the exclusivity incentive program in the Food and Drug Administration Modernization Act (FDAMA) in 1997, approximately 80 percent of medication labels in the Physician's Desk Reference did not have pediatric use information. Similarly, only 20-30 percent of drugs approved by FDA were labeled for pediatric use as evidenced by surveys from 1984-1989 and 1991-2001. In a survey covering 1991-1997, only 38 percent of new drugs potentially useful in pediatrics were labeled for children when initially approved. Many drugs were used "off-label" to treat pediatric patients without any data to establish the correct dose for pediatric patients or to confirm safety or efficacy in the pediatric population.

In 1997, as part of FDAMA, Congress provided marketing incentives to manufacturers who voluntarily conduct studies of drugs in children. This law provides six months of additional market exclusivity for a drug (active moiety) in return for conducting pediatric studies in response to a written request (WR) issued by FDA. To qualify for pediatric exclusivity, the pediatric studies must "fairly respond" to a WR issued by FDA that describes the needed pediatric studies (including, for example, indications to be studied, number of patients, etc).

The incentive, which applies only to those drugs regulated under section 505 of the Federal Food, Drug, and Cosmetic (FD&C) Act, has become the most successful pediatric initiative that the Agency has participated in to date.

In 2002, the pediatric exclusivity incentive was re-authorized in the Best Pharmaceuticals for Children Act (BPCA), a statute that added provisions for safety evaluation of products that received exclusivity, public dissemination of study information, and additional mechanisms for the study of drugs in children that drug sponsors decline to study, including active moieties with no remaining patent or market exclusivity.

In 2003, Congress passed another important law that works in concert with BPCA – the Pediatric Research Equity Act (PREA). PREA provides FDA the authority to require pediatric studies under certain conditions. PREA requires pediatric assessments of drugs and biological products for the same indications previously approved or pending approval when the sponsor submits an application or supplemental application to FDA for a new indication, new dosing regimen, new active ingredient, new dosage form, or new route of administration. PREA codified many provisions of the "Pediatric Rule," a regulation that FDA issued in 1998 that required certain pediatric studies but was struck down by the U.S. District Court for the District of Columbia for exceeding FDA's statutory authority. Both the Pediatric Rule and PREA were designed to work in conjunction with the pediatric exclusivity provisions of FDAMA and the successor provision, BPCA. As with BPCA, PREA has been extremely successful in generating pediatric studies on many drugs and helping to provide important new information in product labeling.

SUCCESS OF BPCA AND PREA

Together, BPCA and PREA have generated pediatric studies on many drugs and helped to provide new information in product labeling. Both statutes continue to foster an environment that promotes pediatric studies and to build an infrastructure for pediatric trials that was previously non-existent. These programs have encouraged the development of important new safety, effectiveness, and dosing information for drugs used in children. They have enabled FDA to obtain important pediatric information and numerous labeling changes.

Since 1997, the exclusivity incentive program has generated labeling changes for 128 products. The labeling changes have significantly increased the information available to health care professionals to use in the treatment of pediatric patients. The labeling for 83 products has been updated to include new information expanding use of the product to a broader pediatric population; the labeling of 25 products had specific dosing adjustments; the labeling of 28 products were changed to show that the products were found **not** to be safe and effective for children; and 37 products had new or enhanced pediatric safety information added to the labeling (these numbers add up to a number greater than 128 because some products had more than one change to the labeling).

Moreover, sponsors have submitted 504 proposed pediatric study requests to FDA, and 341 WRs have been issued by FDA to drug sponsors requesting over 703 pediatric studies (a WR may request more than one study). FDA has made 150 exclusivity determinations and granted exclusivity in 136 of those determinations. The studies conducted under BPCA have

made a significant contribution to the public health as demonstrated by the labeling changes that have resulted from these studies. Also, safety (adverse event) reviews have been presented to the Pediatric Advisory Committee (PAC) for 65 products. In addition, FDA has placed 56 products on the BPCA off-patent priority list and issued 16 WRs for off-patent products to obtain needed pediatric information.

Since PREA was enacted, FDA has approved 496 new drug applications (NDAs) and supplemental NDAs that fell within the scope of PREA (i.e., applications for new active ingredients, new dosage forms, new indications, new routes of administration, or new dosing regimens). These approvals have resulted in approximately 40 labeling changes involving pediatric studies linked to PREA assessments since the enactment of the legislation in 2003. In addition, FDA has approved 58 biologics license applications (BLA) and supplemental BLAs that fell within the scope of PREA.

BPCA & PREA PROCESSES: HOW DO THE PROGRAMS WORK?

BPCA – "On-Patent"

The goal of the BPCA process is to obtain pediatric studies that will enable a sponsor to fully label the drug (active moiety) for pediatric use. The BPCA process applicable to drugs with remaining patent or market exclusivity can be initiated in two ways. FDA, after background research and an extensive literature review, can determine if there is a public health need for additional pediatric studies for a particular drug and issue a WR for such studies. Alternatively, a drug sponsor can initiate the process by submitting a proposed pediatric study

request (PPSR) to FDA suggesting the studies that the sponsor believes are appropriate. FDA will review the PPSR and, as appropriate, can use it as a starting point for drafting the WR. It is important to note that FDA does not issue a WR if we determine there is not a public health need.

CDER has a pediatric team (the Pediatric and Maternal Health Staff) that coordinates CDER's pediatric activities. The review divisions have primary responsibility for drafting WRs. During the drafting process, the review division may consult with the pediatric team. Once drafted, the WR is reviewed by the Pediatric Implementation Team (PdIT). PdIT is composed of individuals from various disciplines within the Agency and members of the pediatric team.

More specifically, after the division develops a WR, the process then continues through the following steps:

- Review by PdIT (with potential additional changes by review division).
- WR Issued – the sponsor has 180 days to respond, accepting or declining.
- If accepted, the sponsor completes the studies and submits them in a priority supplemental application or NDA (the review is subject to Prescription Drug User Fee Act [PDUFA] timelines).
- The Pediatric Exclusivity Board (PEB), an FDA committee, separate from PdIT, also comprised of individuals from various disciplines within the Agency, makes an exclusivity determination within 90 days after submission.

- The reviewing division's scientific reviews of studies submitted to FDA in response to a WR are to be completed within 6 months for priority NDA supplements, and within 10 months for full NDA applications.
- For supplements, summaries of medical and clinical pharmacology reviews are posted on the Web.

While the BPCA process is integrated within the standard process of drug review for pediatric studies submitted in applications or supplements, the implementation of BPCA does have aspects that distinguish it from the standard drug review process, such as:

- all supplemental applications are reviewed as priority under PDUFA goals;
- the exclusivity determination must be made in 90 days; and
- summaries of medical and clinical pharmacology reviews are publicly posted regardless of approval status.

It is important to note that for pediatric studies submitted under BPCA, there are two review processes that occur in parallel: a review to determine if the studies "fairly respond" to the WR, thus qualifying the product for exclusivity; and a review of the supplement or NDA to determine whether the supplement or NDA should be approved under FDA's ordinary review process. Both are carried out by CDER with input from the Office of Pediatric Therapeutics.

BPCA Exclusivity Determination

First, the exclusivity review is conducted after the submission of the studies performed in response to the WR. The scientific division responsible for reviewing the drug being studied initially reviews the submission to determine if the submitted studies "fairly respond" to the WR. Because the division also is charged with review of the scientific aspects of the submission, FDA has found it important that they present their findings to an independent body, the PEB. This board is composed of individuals from multiple components of the Agency including the review divisions, and the Office of General Counsel, among others. Based on the information provided by the division, the PEB either makes a recommendation to grant or deny pediatric exclusivity or requests additional information. Exclusivity is granted (or denied) solely on the basis of whether the studies submitted "fairly respond" to the WR. Under the terms of the statute, the pediatric exclusivity determination must be made within 90 days of the submission of the studies. If the sponsor's submission fairly responds to the WR, is timely submitted, and the studies are conducted in accordance with commonly accepted scientific principles and protocols, FDA will grant the six months pediatric exclusivity at that time.

Because the 90 day timetable for exclusivity determinations is shorter than the timeframe under which the related application or supplement is being reviewed, in most cases, the exclusivity determination for the active moiety will be made before the scientific and medical review of the submitted labeling changes has been completed. It should be noted that an award of pediatric exclusivity does not mean the supplement or the NDA is approved or that it is guaranteed approval. The grant of exclusivity does not depend on approval of the

application or supplement and does not depend on there being a labeling change that results from the studies because exclusivity attaches to the entire moiety and not simply to the particular drug product for which the application or supplement is submitted.

Scientific Review and BPCA

The scientific review of the application (supplement or original NDA) by CDER is subject to the same scientific rigor and administrative terms and conditions as other application reviews. Under BPCA, all supplements submitted in response to a WR are classified as priority reviews, with a six month Prescription Drug User Fee Act (PDUFA) goal date. Timelines are determined according to PDUFA- so the "clock" for review stops and starts depending on the action taken – such as a request for more information from the sponsor or an amendment to the application.

As part of the scientific review of the application, FDA decides whether labeling changes are warranted. FDA includes both positive and negative information from study reports submitted in response to a WR in the labeling because both types of information may be useful to physicians and pharmacists. BPCA includes a dispute resolution process where the FDA can refer labeling disputes to the PAC for decision to ensure timely labeling changes. FDA has been successful in obtaining labeling changes related to pediatric safety and efficacy and has not had to use the dispute resolution process.

BPCA also provides a mechanism for WRs for drugs currently protected by patent or exclusivity to be referred to the Foundation for National Institutes of Health (NIH), if the sponsor declines to conduct the studies included in the WR.

BPCA – "Off-Patent" Process

In 1997, the FDAMA provisions required FDA, after consultation with experts in pediatric research, to develop, prioritize, and publish an initial list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population. FDA published the initial list on May 20, 1998. The list included a number of drugs for which there was no remaining patent or exclusivity. The additional exclusivity was not an incentive for those sponsors with "off-patent" drugs and few of those drugs were studied under that provision.

In response to the need for pediatric studies in many "off-patent" drugs, the reauthorization of the pediatric exclusivity incentive in BPCA included a mechanism to address such studies. Under its provisions, FDA and NIH jointly develop a prioritized list of off-patent drugs for which we believe pediatric studies are needed. This list is published annually in the *Federal Register*. FDA can issue WRs for these drugs under the usual process. If the sponsor declines the WR, FDA can refer the WR to the National Institute for Child Health and Human Development (NICHD) at NIH.

BPCA -- Pediatric Advisory Committee and the Office of Pediatric Therapeutics

The BPCA expanded and enhanced the initial pediatric exclusivity process in two important ways. First, it authorized FDA to establish the Pediatric Advisory Committee (PAC), and provided for post-marketing safety review by PAC of all pediatric products granted exclusivity by FDA. FDA provides PAC with all adverse events received within a one-year period after the product is granted exclusivity so that PAC can do a safety review and provide input to FDA. If appropriate, PAC can make recommendations after its review about things that should be modified in labeling, additional areas for investigation, and even requests for FDA to work with sponsors to obtain additional clinical trial data. The other novel aspect of BPCA is that it promotes transparency by requiring that summaries of the studies conducted under the BPCA be posted regardless of the regulatory action (e.g., approval, non approval).

Second, BPCA created the Office of Pediatric Therapeutics (OPT) which, as part of FDA's Office of the Commissioner, provides scientific expertise and ethics advice, and coordinates and facilitates activities that may have any affect on the pediatric population or the practice of pediatric medicine, or may involve pediatric issues. The office includes an ethicist specializing in pediatric ethics to assist in its responsibilities. OPT manages PAC and coordinates the review by PAC of adverse event reports for drugs granted pediatric exclusivity. OPT also coordinates and provides liaison activities both with internal FDA/Department of Health and Human Services offices and groups, and with external groups, including international organizations.

PREA PROCESS

In contrast to BPCA, which provides a voluntary mechanism for obtaining needed studies on either approved or unapproved indications for a given drug, PREA requires pediatric assessments (based on studies in pediatric populations) of certain drugs and biological products, but only in the indications that are approved or for which the sponsor is seeking approval, and only under certain circumstances. PREA is triggered when an application or supplement is submitted for a new indication, new dosing regimen, new active ingredient, new dosage form, and/or a new route of administration. It also can be invoked by FDA for a product for which an application or supplement is not being submitted if a WR issued under BPCA has been declined by the sponsor and other BPCA-created mechanisms to obtain the studies have been exhausted. PREA includes provisions allowing FDA to defer or waive the required pediatric assessments under limited circumstances.

Also, in contrast to BPCA, PREA applies not just to NDAs but also to BLAs. Thus, CDER and CBER are both responsible for implementation of PREA, while CDER is the only Center in FDA that implements BPCA. Sponsors develop a *pediatric plan* - a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that the applicant plans to conduct and addresses the development of an age-appropriate formulation and whether, if so, what grounds, the applicant plans to request a waiver or deferral under PREA.

Applicants are encouraged to submit their pediatric plans, and information to support any planned request for waiver or deferral, as early as possible in the drug development process and to discuss these plans at critical points in the development process for a particular drug or biologic. In each Center, for products for life-threatening diseases, the appropriate review division will provide its best judgment at the end of Phase I (the first phase of clinical studies involving human subjects) meetings on whether pediatric studies will be required under PREA and whether the submission will be deferred. For products not intended for life-threatening or severely debilitating illnesses, applicants are encouraged to submit and discuss their pediatric plan no later than end of Phase II meeting. The review divisions that handle that particular drug or biologic provide their best judgment about (1) whether a pediatric assessment is required, (2) whether its submission can be deferred or waived, and (3) if deferred, the date studies should be due.

FDA can grant a deferral under PREA when the product is ready for approval in adults but the pediatric studies have not been completed; when additional safety and effectiveness information in adults is needed before beginning studies in children; or there is another appropriate reason for deferral. The PREA requirements also can be waived either in full or in part. Full waivers, covering the entire pediatric population, are granted when the necessary studies are impossible or highly impracticable (such as, for example, when a disease or condition does not ordinarily occur in children); evidence strongly suggests the product would be ineffective or unsafe in children; or the drug or biologic does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients. Partial waivers are granted when these same criteria

apply only to a subset of the pediatric population, or when the sponsor can demonstrate that it has made reasonable attempts to produce a pediatric formulation, but that its efforts have failed. PREA specifically requires that, if a full or partial waiver is granted because available evidence suggests a product would be unsafe or ineffective in children, this information must be included in the labeling for the product.

CONCLUSION

The number of pediatric clinical trials for FDA-regulated products has increased dramatically since 1997 and has resulted in the development of invaluable efficacy, safety, and dosing information regarding the use of these products in the pediatric population. BPCA and PREA work in tandem to encourage and require pediatric studies that are vital to the health and welfare of this important population. PREA helps to fill the need for those studies not addressed by BPCA, and we believe that it is important to keep these programs working side by side. We would like to see the programs continue to succeed in years to come.

The incentives provided by BPCA should continue to lead to significant advances in pediatric medicine. It is important to have that wide reaching but voluntary program balanced with the more limited but mandatory studies that can be obtained under PREA. The two statutes have acted in concert to provide important safety, efficacy, and dosing information for drugs used in children. FDA wants to build on these improvements with more studies to produce new labeling information that is of value in treating children.

Despite the successes of these two programs, there is more work to be done. There are still a large number of drug and biological products that are inadequately labeled for children. More broadly, long-term safety and effects on growth, learning, and behavior are critically important to safe use of certain medications and continue to be understudied. Due to technical challenges and the need for sequential studies, neonates also still remain mostly unstudied and little is known about the safety and efficacy of the therapies being used to treat them. These issues are still of concern, as it is this youngest population that is undergoing marked physiologic and developmental changes, which are affected by drug therapies. FDA intends to persist until these are all studied.

FDA welcomes the opportunity to work with Congress to ensure that the benefits of an incentive program can continue, in conjunction with FDA's authority to require mandatory studies, as Congress considers the reauthorization of the BPCA and PREA programs. Thank you for sharing our interest in pediatric medicine and the health of our children.

Mr. PALLONE. Thank you, Dr. Kweder. Dr. Mattison.

STATEMENT OF DONALD MATTISON, M.D., CHIEF, OBSTETRIC AND PEDIATRIC PHARMACOLOGY BRANCH AND HUMAN DEVELOPMENT, NATIONAL INSTITUTES OF HEALTH

Dr. MATTISON. Good morning, Mr. Chairman. I am Donald Mattison, Chief of the Obstetric and Pediatric Pharmacology Research Branch at the National Institute of Child Health and Human Development, the National Institutes of Health. We appreciate the opportunity to appear before you and the rest of the committee to discuss NIH's research activities in relation to implementation of the pediatric drug testing program under the Best Pharmaceuticals for Children Act.

The BPCA legislation was enacted in 2002 to address the growing recognition that the great majority of pharmaceutical products prescribed for children have never been tested for pediatric use. Healthcare professionals were forced to depend upon experience and their best judgment in prescribing medications for their pediatric patients. However, without a strong evidentiary base, it becomes difficult for practitioners to work with children of various ages who are at various developmental stages to estimate what the correct dose should be. Since children metabolize or respond to a drug differently from an adult, that drug's effect may be variable with too high a dose producing toxicity, too low a dose being ineffective to treat the child's disease.

Under current law, the NIH is directed to conduct research-related activities in three general categories, identifying and prioritizing drugs needing study in children, developing new study requests in collaboration with the Food and Drug Administration and other pediatric experts, and supporting studies on priority drugs after manufacturers decline to do so. In most cases, the drugs under consideration for study by the NIH are for off-patent or older medications to which no marketing exclusivity can be granted. In some instances, these medicines have been used for over 30 years and yet, those same efficacy and safety information have not been compiled for children.

This is a challenging area of research. The available data are mostly on adults. Some of the conditions that these drugs are used to treat are relatively rare, and effects on children's growth and development have largely been unrecognized and certainly can't be studied in adults. In addition, human subjects concerns with a critical focus on balancing risks versus benefits are of particular importance in pediatric research. Moreover, long-term follow-up of the possible effects on growth and development can be important but costly aspects of pediatric clinical trials. To conduct these studies and obtain generalizable data, we often need to enroll a larger number of pediatric patients than have previously been studied. In order to prioritize the drugs needing studies, NICHD has developed an annual cycle of data gathering, expert consultation, and critical analysis. The purpose of the process is to distill from the total number of off-patent drugs to a manageable number, five to 10, for study the following year. We look at whether dosing, safety, and efficacy data are already available from a reputable source and whether additional data are needed, whether new studies will

produce health benefits for children, and the balance between how frequently the condition is to be treated and the severity of the condition, whether there is a need to reformulate the drug so that children will be able to use it. As an example, a drug that only comes in tablet form cannot be readily taken by a young child with cerebral palsy. Together with other NIH institutes and centers, the FDA and other pediatric experts, NICHD has made significant progress on this front as required by BPCA by developing and publishing an annual list of approved drugs in need of further study in pediatric populations. As of December 2006, 106 total drugs have been addressed and discussed in scientific forums to decide if they should be listed or whether we need further review of medical literature or outside consultation. From this group of drugs, approximately 60 drug indication pairs have been listed as off-patent priority drugs, drugs that require further pediatric studies. I have provided a list of those drugs to the committee in table 1.

From the list of prioritized drugs, the FDA, in consultation with the NIH, develops and issues written requests to the drug manufacturers. To date, 16 written requests have been developed and forwarded to the manufacturers by the FDA. All but one of those written requests have been declined by the manufacturer, and those drugs have been referred to the NIH for study. Since receiving the 16 written requests, we have implemented, as shown on table 2, 13 drug studies that we are currently conducting and funding with support from other NIH institutes and centers that have significant pediatric research programs.

BPCA implementation is a trans-NIH collaboration with 19 NIH institutes and centers investing more than $25 million annually. While many of the projects first funded after the enactment of the BPCA are in their final years of funding and results are expected in the next few years, we have learned a great deal of pediatric pharmacology and reach out regularly to the field to further understand the needs of clinicians who treat children. For example, research findings suggest the need for testing a variety of drugs and other approaches to address the increasing problem of obesity-related hypertension in adolescents and improving the health of these young people. We have also organized and invited experts to numerous workshops on a myriad of issues that surround pediatric studies, including formulations for use at different stages of development, the design requirements and ethics of clinical trials in this special population.

Some of what we have learned has been unexpected. Information on a number of drugs which we thought initially would require only late phase III or phase IV clinical trials in children to provide the data we were seeking, proved completely inadequate; and we were forced to revise our plans and fund more preliminary studies on safety and efficacy. A number of those studies are underway.

In summary, significant progress has been made to establish the infrastructure and support for pediatric drug studies that can provide critical information regarding the safe and effective use of these medications in children. We look forward to continuing to work with this important committee and would be happy to answer any questions you and other members of the committee might have. Thank you.

[The prepared statement of Dr. Mattison follows:]

STATEMENT OF DONALD MATTISON, MD

Good morning, Mr. Chairman. I am Donald Mattison, chief of the Obstetric and Pediatric Pharmacology Research Branch at the National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH). We appreciate the opportunity to appear before you and the rest of the Committee to discuss NIH's research activities in relation to implementation of the pediatric drug testing program under the Best Pharmaceuticals for Children Act (BPCA).

The BPCA legislation was enacted in 2002 to address the growing recognition that the great majority of pharmaceutical drugs prescribed for children had never been tested for pediatric use. Health care professionals were forced to depend upon experience and their best judgment in prescribing medications for their pediatric patients. However, without a strong evidentiary base, it becomes difficult for practitioners who work with children of various ages who are at a range of developmental stages to estimate what the correct dose may be. Since children may metabolize or respond to a drug differently from an adult, that drug's effects may be variable—too high a dose for a given child poses risks of toxicity, too low a dose may be ineffective.

Under current law, the NIH is directed to conduct research-related activities in three general categories: identifying and prioritizing those drugs needing study in children, developing new study requests in collaboration with the Food and Drug Administration (FDA) and other pediatric experts, and supporting studies on priority drugs after manufacturers decline to do so. In most cases, the drugs under consideration for study by the NIH are for off-patent or older medications for which no marketing exclusivity can be granted. In some instances, these medications have been in use for over thirty years, and yet relative dosing, efficacy and safety data have yet to be compiled for children.

This is a challenging area of research. The available data are mostly on adults; some of the conditions these drugs are used to treat are relatively rare; effects on children's growth and development have been largely unrecognized and certainly cannot be studied in adults. In addition, human subjects concerns, with a critical focus on balancing risks versus benefits, are of particular importance in pediatric research. Moreover, long-term follow-up of the possible effects on growth and development can be an important, but costly, aspect of pediatric clinical trials. To conduct these studies and obtain generalizable data, we often need to enroll larger numbers of pediatric patients than have been previously studied.

In order to prioritize the drugs needing study, NICHD has developed an annual cycle of data gathering, expert consultation and critical analysis. The purpose of the process is to distill, from the total number of off-patent drugs (approximately 200) to a manageable number (five to ten) for study in the following year. We look at whether dosing, safety and efficacy data are already available from a reputable source and whether additional data are needed, whether new studies will produce health benefits for some subpopulation of children, the balance between how frequently the condition to be treated may occur and the severity of the condition, and whether there is a need to reformulate a drug so that children will be able to use it. For example, a drug that only comes in tablet form cannot readily be taken by an infant or by a young child with cerebral palsy.

Together with other NIH Institutes and Centers, the FDA, and other pediatric experts, the NICHD has made significant progress on this front—as required by the BPCA—by developing and publishing an annual list of approved drugs in need of further study in the pediatric population. As of December 2006, 106 total drugs have been discussed in a scientific forum to decide if they should be listed, or whether we need further review of the medical literature or outside consultation. From this group of drugs, approximately 60 drug/indication pairs have been listed as off-patent priority drugs that require further pediatric studies. These annual lists have been provided to the committee in Table 1.

From each list of prioritized drugs, the FDA, in consultation with the NIH, develops and issues a series of Written Requests to the drugs' manufacturers; to date, all but one has been declined by the manufacturer, and the drugs have been referred to the NIH for study. Table 2 shows the 13 drug studies the NIH is currently funding and the status of each. We could not be conducting this work without the scientific expertise and financial support from the other NIH Institutes and Centers that have significant pediatric research portfolios. BPCA implementation is a major trans-NIH collaboration, as 19 NIH Institutes and Centers are investing more than $25 million annually.

While many of the projects first funded after the enactment of the BPCA are in their final year(s) of funding and results are expected in the next few years, since the enactment of BPCA, we have learned a great deal about the field of pediatric pharmacology and reach out regularly to the field to better understand the needs of the clinicians who treat children. For example, research findings suggest a need for testing a variety of drugs and other approaches to address the increasing problem of obesity-related hypertension in adolescents (high blood pressure related to weight gain), and improving the health of these young people. We also have organized and invited experts to numerous workshops on the myriad of issues that surround pediatric studies, including formulations for use at different stages of development, the design requirements and ethics of clinical trials in this special population.

Some of what we learned was unexpected. Information on a number of drugs, which we initially thought would require only Phase III or IV clinical trials in children to provide the data we were seeking, proved to be completely inadequate, and we were forced to revise our plans and fund more preliminary studies on safety and efficacy. A number of those studies are now underway.

In summary, significant progress has been made to establish the infrastructure and support for pediatric drug studies that can provide critical information regarding the safe use of these medications in children. We look forward to continuing this important work, and I would be happy to answer any questions you or the other members of the committee may have.

TABLE 1

2003:
Ampicillin/Sulbactam: treatment of pediatric infections
Azithromycin:
- Prevention of bronchopulmonary dysplasia in infants with Ureaplasma urealyticum
- Prevention and treatment of Chlamydia conjunctivitis and pneumonia

Baclofen: treatment of spasticity in children with cerebral palsy
Bumetanide: treatment of pediatric hypertension
Diazoxide: treatment of hypoglycemia in children
Dobutamine: treatment of hypotension and low cardiac output in children
Dopamine: treatment of hypotension and low cardiac output in children
Furosemide: treatment of pediatric hypertension
Heparin: prevent blood clotting in children
Isofluorane: produce general anesthesia in children
Lindane: treatment of lice and scabies in children
Lithium: treatment of mania in children with bipolar disorder
Lorazepam:
- Treatment of status epilepticus in children
- Provide sedation for children in intensive care being treated with a respirator

Meropenem: treatment of pediatric infections
Metoclopramide: treatment of children with Gastroesophageal reflux
Piperacillin/Tazobactam: treatment of pediatric infections
Promethazine: treatment of nausea and vomiting in children
Rifampin:
- Treatment of Methicillin resistant Staphylococcus aureus endocarditis in children
- Treatment of central nervous system shunt infections in children

Sodium Nitroprusside: produce hypotension in children undergoing surgery to reduce blood loss
Spironolactone: treatment of pediatric hypertension

2004:—
Ampicillin: treatment of pediatric infections
Dactinomycin: treatment of pediatric cancer
Ketamine: sedation of children for short procedures
Metolazone: treatment of pediatric hypertension
Vincristine: treatment of pediatric cancer

2005:—
Acyclovir: treatment of pediatric infections with herpes
Clonidine:
- Treatment of autism in children
- Treatment of ADHD in children

Cyclosporine: prevention of organ transplant rejection in children

Ethambutol: treatment of children with tuberculosis infections
Flecanide: treatment of cardiac arrhythmias in children
Griseofulvin: treatment of Tinea capitis infections in children
Hydrochlorothiazide: treatment of pediatric hypertension
Hydrocortisone valerate: treatment of inflammatory skin conditions in children
Hydroxychloroquine: treatment of connective tissue disorders in children
Ivermectin: treatment of scabies infection in children
Methadone: treatment of neonates undergoing opioid withdrawal
Sevelamer: treatment of hyperphosphatemia in children with chronic renal failure
Morphine: treatment of pain in pediatric patients

2006:
Albendazole: treatment of children with parasitic infections
Amantidine: treatment of children with influenza
Daunomycin: treatment of children with cancer
Guanfacine: treatment of children with ADHD
Methotrexate: treatment of children with cancer
Mebendazole: treatment of children with parasitic infections
Pralidoxime: treatment of children with organophosphate poisoning
Rimantadine: treatment of children with influenza
Hydroxyurea: treatment of children with sickle cell disease to prevent painful blood sickling crisis
Methylphenidate: characterize safety in this drug used to treat children with ADHD

Table 2
The following pediatric drug studies currently are being supported with NIH funding:

- Lorazepam—Phase I, Phase II and Phase III clinical studies to support treatment for status epilepticus (NINDS)
- Lorazepam—Phase I, Phase II and Phase III clinical studies to support sedation of children on respirators in an intensive care unit
- Nitroprusside—Phase I, Phase II and Phase III clinical studies to understand use to reduce blood pressure during surgery to reduce blood loss
- Lithium— Phase I, Phase II and Phase III clinical studies to define treatment of mania in children with bipolar disorder (NIMH)
- Baclofen—Phase I, Phase II and Phase III clinical studies to understand oral treatment of spasticity, most commonly from cerebral palsy
- Vincristine—Phase I, Phase II and Phase III clinical studies to enhance treatment for malignancies in children (NCI)
- Dactinomycin—Phase I, Phase II and Phase III clinical studies to enhance treatment for malignancies in children (NCI)
- Daunomycin—Pharmacokinetics, safety, efficacy of daunomycin to treat childhood cancers and relationship to body weight (NCI)
- Methotrexate—Phase II and Phase III clinical studies to improve treatment outcomes for pediatric patients with high risk acute lymphoblastic leukemia (NCI)
- Ketamine—Preclinical studies to evaluate the scientific and safety concerns about the use as an anesthetic in children
- Hydroxyurea—Preclinical, Phase I, Phase II and Phase III clinical studies to improve treatment of children with sickle cell disease (NHLBI)
- Methylphenidate—Preclinical and clinical evaluation of pharmacokinetics and safety to understand reports of cytogenetic toxicity (NIEHS)
- Morphine—preclinical basic science evaluations of the developmental expression of opioid receptors to better understand management of pain in children of different developmental stages and safety issues in treating pain in neonates

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Mr. PALLONE. Thank you, Dr. Mattison. We will move to questions now, and I will start by recognizing myself for 5 minutes.

I wanted to talk about the pediatric exclusivity. Dr. Kweder, as you are aware, there is some concern within Congress that there are economic incentives associated with BPCA that encourage drug sponsors to provide pediatric studies on those drugs that are most widely used in adult populations, the so-called blockbuster drugs. Furthermore, according to an article that appeared in the Journal

of the American Medical Association, the value of the patent extensions under BPCA was often greater than the costs of conducting the pediatric studies requested by the FDA. Some of these drugs received as much as $508 million return because of the 6-month extension. The Senate, dare I mention the other body, included in their bill recently reauthorizing BPCA and PREA a provision that scaled back at the amount of exclusivity a company could get based on its earnings. For drugs whose annual earnings exceed $1 billion, they would get 3 additional months of exclusivity for conducting pediatric trials requested by FDA. I just want to know if that is something the administration supports and why or why not.

Dr. KWEDER. I can comment generally on this. I am well-aware of the article that really set out to look at the cost of doing the trials themselves versus the exclusivity. What that study could not do and one of the things that we are faced with doing is before we issue such a request, we look very carefully to ensure that any written request that we issue, any specific request for a trial or set of trials, it is often more than one, that would lead to exclusivity is something that will have a meaningful public health benefit for children. The questions that will be answered in those trials will result in something meaningful to the public health. Unfortunately it is really difficult to assign a dollar amount to bump the public health benefit; and that is what we are faced with. Remember that in some cases, these are going to be for products that are manufactured by large companies that have wide use in adults and are being used for a number of different things that are different from adults than for pediatric patients. In other cases we are dealing with a company that has one drug that has a very small niche but we see an important pediatric need.

We have not been in a position where we have had to make those determinations of what is the sponsor likely to get out of this.

Mr. PALLONE. You seem to be telling me that your decisions do not in anyway reflect whether——

Dr. KWEDER. Our decisions do not take into account how much money they make today or are likely to make in the future. If you were to decide that was something we needed to do, we would certainly have to work to obtain some expertise in helping us make those assessments. Our concern is that that may end up delaying the process in some ways.

Mr. PALLONE. All right. So you don't really want to link your decision to the money, but then you are really not taking a position on the 3 months it seems to me, right?

Dr. KWEDER. No, I am not taking a position. I will say to give you a flavor of how seriously we take this public health benefit, if you look at the numbers—I mentioned that sometimes a company can initiate a request. We have had well over 500 of those come from companies.

Mr. PALLONE. OK.

Dr. KWEDER. We have only issued like 350, 375, but for over 700 studies, which tells you that we don't take the company's initial request at face value. We are really looking harder. They complain because our requirements are too tough.

Mr. PALLONE. OK. That is fair. Let me get to my next question. As I understand it, there are different labeling requirements that

apply when a drug maker applies to FDA for approval to list a pediatric indication of a new drug versus when a manufacturer received exclusivity after conducting appropriate studies. Under the first case, pediatric use information is included in the labeling only if FDA approved the pediatric indication. If FDA turned down or the manufacturer withdrew a request for an indication, not only does pediatric use information not appear in the product's labeling the fact that the manufacturer had made an unsuccessful attempt and the research findings that blocked the approval—neither are noted in the label, nor made public in other ways. But under exclusivity rules, information goes on the label regardless of whether or not a drug is found to be appropriate for pediatric use. I am concerned by this disconnect. Shouldn't information regarding pediatric use be made available to the public regardless of whether we learn about it when a drug manufacturer applies for a pediatric indication or through the exclusivity rules? Wouldn't it be helpful for physicians or parents to know whether or not a drug maker applied to have their drug approved for pediatric indications and was denied and would the administration be supportive of changing the rules to accomplish that?

Dr. KWEDER. Let me say that we take the need for inclusion of information about use of a product in pediatrics very seriously, and where we have data that specifically suggests that there may be a risk in pediatrics or that a drug may not be effective in pediatric population, we will include that in the label, regardless of whether the request came to us under an exclusivity, through an exclusivity study, or as part of our general application. We are increasingly pushing the envelope on that and ensuring that the public has that information. That is for approved drugs.

Mr. PALLONE. Right.

Dr. KWEDER. Now, the difference under BPCA is that even if an application is not approved under BPCA, a study summary does appear on the web that lets people know about that oftentimes before we even get into the label. But we are increasingly successful in including all that important information for practitioners in product labels and the public in product labels.

Mr. PALLONE. But then if we change the law to make the information more available or to require it and to eliminate this disconnect, you don't have a problem with that?

Dr. KWEDER. We are strongly in favor of transparency.

Mr. PALLONE. OK. All right. Thanks a lot. Mr. Deal.

Mr. DEAL. When a manufacturer initiates the request, you don't take them up on the offer——

Dr. KWEDER. Sometimes we do but we usually modify a lot.

Mr. DEAL. Let us assume you don't take them up at all. Do you have any idea how many of them go forward on their own initiative at that point to do pediatric testing?

Dr. KWEDER. I do not have the answer to that question off the top of my head. That is information I can get you and follow up unless one of my colleagues knows. No, they don't know specifically. Very few. I would say, Mr. Deal, my best estimate is that very few, very, very few.

Mr. DEAL. So the exclusivity is a real useful tool?

Dr. KWEDER. It is an extraordinarily useful tool for us, yes.

Mr. DEAL. Dr. Mattison, let me ask you with regard to your off-patent further investigations, who makes the determination to select those drugs? Is there a scientific panel, is there public input into that process? How do you go about selecting those drugs?

Dr. MATTISON. We have established a process by which we work with the FDA to identify the drugs that are considered to be off-patent; and then on an annual basis, we have pulled together 30 to 50 experts in pediatrics to help us discuss the drugs that we think have the greatest potential for improving public health benefit, in children or have the widest gap between what we know and what we would like to know in terms of the use of those drugs in children. We rely very, very heavily in the set of activities that lead up to selecting drugs on input from experts from around the United States in pediatrics, our colleagues in the various institutes and centers of the NIH that participate in BPCA, as well as our colleagues at the FDA. So this is a very open, deliberative process that we believe helps us identify those drugs for which testing will have a substantial impact on children's health.

Mr. DEAL. With regard to those tests, are most of those tests conducted within the institute or are they contracted out through grant programs? How do you conduct them?

Dr. MATTISON. The tests are all financed by the institutes but conducted outside of the NIH through grants and contracts, and the choice of the mechanism that we use depends upon the nature of the study that we are interested in performing. For large clinical trials, we have used a contract as a way of assuring that the various institutions that participate understand what we specifically need from the clinical trial to improve how the drug is used or thought about in children. In some instances we have been surprised by the lack of even basic science knowledge about the drugs, and in that case we have used grants as the mechanism to build the scientific understanding that we need before we can actually design the clinical trail.

Mr. DEAL. Let us take a situation in which you have done one of these tests to further determine the applicability of a drug for pediatric usage that was not initially approved by FDA. Do you find at that point that the manufacturers of those drugs take your information and then go back to FDA for relabeling or new applications? What is the process that follows your research?

Dr. MATTISON. When the research is completed and the data has been analyzed from the clinical trials, that data is made publicly available as a part of the FDA docket system so that any investigator from around the United States or anywhere around the world could actually take a look at the outcomes of those clinical trials and determine whether or not they thought it was appropriate to use that drug in children. As I understand the current BPCA law, the manufacturers can't get additional exclusivity. We haven't encountered the issue of the manufacturers asking to use the data, but we make the data publicly available to anyone that would like to take a look at it.

Mr. DEAL. But it would seem to me to logically close the loop, they would go back to FDA and apply for new application for usage for pediatric purposes. Is that what happens, Dr. Kweder?

Dr. KWEDER. Yes, if it were important information to come from any of those studies, we absolutely would ensure that it made it to product labeling. Oftentimes you are dealing with a generic product that has multiple manufacturers, for example; but we would make sure that those data were widely available in a package insert.

Mr. DEAL. But is there enough interest on the part of either the initial innovator product or the follow-on generics? Do they have enough interest in this to initiate it?

Dr. KWEDER. Seek to initiate it? I think it is quite variable, particularly if there is a safety issue. They will usually see that it is in their best interest to include that information in their labeling, but we have managed to find ways to require them to include that information.

Mr. DEAL. OK. Thank you.

Mr. PALLONE. Mr. Waxman.

Mr. WAXMAN. Thank you very much, Mr. Chairman. When we give the exclusivity, we are giving what could be a very rich reward, and it seems to me that we want to make sure that we are getting something well worthwhile in return. There are many drugs with annual U.S. sales in the billions, so when we are talking about an extra 6 months of exclusivity paid for by the uninsured, the Federal Government, businesses, and insurers in the form of higher monopoly drug prices, we want to see if that price tag was worth it.

Dr. Kweder, in your testimony you said that since BPCA's inception in 1997, FDA has made 150 exclusivity determinations and has awarded exclusivity in 136 of those cases. Your testimony also describes the process by which FDA makes the decision to award exclusivity. Essentially you base that decision on a brief and cursory review of the submitted studies, looking only at whether they fairly respond to the terms of the written request. That decision is not based upon the latter and more thorough scientific review of the studies which forms the basis for your decisions about what FDA will actually do with the information contained in the studies. You obviously award exclusivity in most cases based on the first preliminary review, so I assume it is only companies who fail egregiously to comply with the terms of the written request that are denied exclusivity. Can you briefly give a couple of examples of cases in which FDA denied exclusivity?

Dr. KWEDER. One thing that I think is important to understand is the reason that we make that determination of exclusivity in advance of the scientific review is that BPCA requires to us to render a decision on exclusivity at 90 days after the application is submitted. 90 days. For a priority review, scientific review, under our current user fee legislation, we have 6 months to complete our review. And sometimes the decision about—many times the exclusivity determination is relatively easy to make where you can quickly get a good sense of the data in the application, but the types of—and some of the cases where we denied exclusivity is because it is very clear on its face that we asked for a study of a certain size and the company came in with a study a fraction of the size that we had already made very clear in our written request, would never be able to provide us meaningful information. That is common.

The more difficult areas where we struggle with the 90 days versus the 6 months is where we are trying to make an assessment about the quality in the way the study was conducted. It is extremely difficult to do that within 90 days in many cases. It may require us to do an inspection of one of the clinical trial sites to really delve into more detail or obtain more data from the sponsor of the application. We have had one situation I can think of where we did deny exclusivity for that reason. It was difficult for us to get to that determination in 90 days, but we were able to do it because we thought that the study was very poorly conducted.

Mr. WAXMAN. You describe instances in which you would have reversed your decision to avoid exclusivity after having conducted the more extensive scientific review of the studies. GAO's report describes an instance in which FDA awarded exclusivity only to later find the children participating in the study had not actually received the treatments as the drug sponsor had claimed in the description of the study.

Dr. KWEDER. Yes, I was trying to remember what the drug was. There was one asthma drug for example where we did award exclusivity. A study appeared to have been conducted well, the size was OK, the population was right. They seemed to have done all the things that we asked for.

Mr. WAXMAN. But rather than talking about one alone because I see my time is running out, are there instances in which you would have reversed your decision——

Dr. KWEDER. Yes, this is one. Yes, this is definitely one, yes, because when we got into the data in more detail we found significant problems with the findings of the data that indicated the study had been not conducted well.

Mr. WAXMAN. OK. I want to ask Dr. Mattison, the GAO report lists some of the studies that NIH is currently conducting and the spending NIH anticipates on those studies. Most of the studies listed were under $10 million, and several were in the $1 to $2 million range. Is it fair to say that those amounts are typical costs for pediatric studies both for NIH and companies that undertake this research?

Dr. MATTISON. Those are the costs that we have been able to negotiate with the various investigators, depending upon the nature of the study. I can't comment on how companies would negotiate with investigators to conduct their studies.

Mr. WAXMAN. They wouldn't do anything all that much different, would they?

Dr. MATTISON. They would be doing similar ones, that is correct.

Mr. WAXMAN. OK. Thank you. Thank you, Mr. Chairman. I see my time is expired.

Mr. PALLONE. Mr. Burgess.

Mr. BURGESS. Thank you. Dr. Mattison, in your written and your oral testimony, you state that some of what we learned was unexpected, information on a number of drugs which we initially thought would require only phase III or phase IV proved to be completely inadequate. We were forced to revise our plans and add a few more preliminary studies. So in some instances you would have to go back and essentially recreate the entire phase I, phase II,

phase III, phase IV study for a particular drug? How does the NIH fund that?

Dr. MATTISON. The funding for all of the studies that we have conducted under BPCA has come from a series of contributions from the 19 institutes and centers that partner with us in the BPCA-related activity. Their partnership was determined based on the size of their pediatric research portfolios. So it is a group of contributions that have come from the various institutes and centers.

Mr. BURGESS. Are there examples from what you provided in table 1 of some of those compounds where you had to literally go back to the beginning and recapitulate the entire study?

Dr. MATTISON. That is correct, and I can give you several examples. In one instance, we have had extensive meetings with pediatric cardiologists, both in the United States and around the world about two commonly used drugs used in the neonatal intensive care unit, dopamine and dobutamine, drugs that are used variously to increase blood pressure or increase profusion through organs; and based on extensive discussions with these pediatric cardiologists, we have been unable to arrive at a scientifically credible clinical trial design. So we have decided that we needed to go back and better understand how those drugs work in the newborn. We do have a pretty good understanding of how those drugs work in adults, but that understanding hasn't translated to an improved understanding.

Another example is morphine, a drug that has been used extensively and is off-patent, 30, 40, 50, 75 years, very, very extensively used. We have data suggesting that morphine alters the way the children's brains respond to trauma during development, and so we have elected to try to understand better the expression of receptors for that drug, rather than to embark on the clinical trials.

Mr. BURGESS. Is any of the body of evidence that has been collected over the last say 70 years in the instance of morphine, is any of that useful to you or do you simply have to start anew?

Dr. MATTISON. Well, it is very useful because we are beginning to understand the receptors that morphine interacts with in terms of producing its effect. What it doesn't help us with is understanding how those receptors are expressed across the course of development in children and whether they are expressed the same way centrally in the brain or in the central part of the body or peripherally.

Mr. BURGESS. That is a fascinating subject. I would actually like to talk to you about that in greater detail, but I don't have time.

Dr. Kweder, in your testimony, you talked about the PREA process. You mentioned just almost in passing that some of these things would apply to biologics also. Now, it is not really part of this hearing but we are at some point going to be asked to issue guidelines on what are so-called biosimilar products or follow-on biologics and is it your feeling that these two would have to, these follow-on or biosimilar products, would need to be exposed to the same types of rigorous study, in some instances even going back to the beginning for biologists in use in children?

Dr. KWEDER. You are asking me several things. Let me just say it is a bit of a frustration for us that we can't utilize BPCA and

biologic therapeutics. As clinicians, doctors don't make a distinction in their treatment needs based on whether it is a biological or a small molecule drug. That is an invisible distinction in the practice of medicine. And so to the practicing clinician, the distinction we have to make is a bit artificial. There are many biological products that we regulate that have potentially very important uses in children.

Mr. BURGESS. But does the concept of having to approve and provide the certification of safety for a follow-on biologic for use in the pediatric population, is this of necessity going to take you back further in that research timeline?

Dr. KWEDER. I am not sure it necessarily will. I mean, these would be basically like generic, what we consider generic products. We don't have these requirements necessarily for generics. We can utilize BPCA if we elect to but——

Mr. BURGESS. If we go to Dr. Mattison, the list in table 1, I mean, it is basically all generics.

Dr. KWEDER. Right, because they are old products, off-patent.

Mr. BURGESS. Correct.

Dr. KWEDER. Right.

Mr. BURGESS. And he has found that it was necessary to get back to step one.

Dr. KWEDER. And we may indeed have to. We may certainly have to go back to some very basic science in studying these biological products in children simply because of the way that they act, their mechanisms of action.

Mr. BURGESS. All right. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. Ms. Eshoo.

Ms. ESHOO. Thank you for recognizing me, Mr. Chairman. As we are asking questions and reviewing the potential for changes to the reauthorizations of this bill, I couldn't help but think that elsewhere in the capitol there is a national summit on America's children taking place which is I think the first time in at least a decade that the intelligencia of our country have gathered relative to America's children, and I can't help but think that what we are doing here obviously is for them as well. So I think that this is a good day here in the Congress.

Dr. Kweder, I wanted to go back to the exchange that you had with Mr. Waxman when you spoke about the 90 days. In your view, does that need to be adjusted? Do you need more than 90 days?

Dr. KWEDER. In some cases we would have been very happy to have more than 90 days to make that determination.

Ms. ESHOO. Is it important enough to change it when you say "some"?

Dr. KWEDER. Yes.

Ms. ESHOO. OK. I think that you both agree that FDA's authority to require pediatric studies should be permanent in PREA? Do you? I am making that assumption. I don't know whether you agree.

Dr. KWEDER. I can't imagine that we would have any objection but that is certainly up to you.

Ms. ESHOO. Well, that sounds kind of medium-rare to me. Well, I understand who the legislators are but we have the experts here to help guide us in making policy.

Dr. KWEDER. May I add to that? We are as I have said in my oral testimony, we are just beginning and it is positive to really fully utilize these tools, and we think that they offer enormous potential and look forward to their continuation.

Ms. ESHOO. I think that there were some questions earlier on the Senate blockbuster provision or an extension of the current 6-month exclusivity. Would you like to comment on that, Dr. Mattison?

Dr. MATTISON. Not from the NIH's perspective, no.

Ms. ESHOO. Not from the NIH's? And Dr. Kweder, you don't have anything further to comment on?

Dr. KWEDER. My comment is that this program has worked extraordinarily well. The opportunity to offer exclusivity in exchange for something that we determine, and we are very particular about this, will have a meaningful public health benefit to pediatrics has been probably what has been the most useful tool that we have had to encourage pediatric drug development, ever. We have been able to utilize the exclusivity provision not just to get information about drug A in a particular narrow indication but as Dr. Mattison has implied, we have utilized it to build a field of pediatric research and answer broader questions that will ultimately apply to more than one product.

Ms. ESHOO. Well, I worked very hard on that part of the legislation to motivate the outcomes that we were looking for so what you are saying is reinforcing it. On labeling, are there any instances where as a result of pediatric studies FDA has requested labeling changes be made to a product and where the drug sponsor has not complied and if so, how did you handle these situations?

Dr. KWEDER. We have been very successful in getting pediatric labeling changes. Some of them have taken longer than we would have liked. Some cases it is because we need more information, but the legislation does provide for us if we are having difficulty getting something in labeling to take it to the Pediatric Advisory Committee. We have not had to take anything.

Ms. ESHOO. Do you need any additional authority in that——

Dr. KWEDER. We have been successful to date.

Ms. ESHOO. So you are saying you don't need any additional authority? Are there any instances, this is on pediatric formulations, where pediatric formulations such as syrup or where a chewable tablet has been developed but not marketed?

Dr. KWEDER. One of the big problems that we have is sometimes there have been examples where a product has been developed for use in a clinical trial, a very small batch that you use on a few patients. But the problem has come where when you try to scale up manufacturing to make something widely available on the market, everything changes. That is a common problem in manufacturing and that is why the biggest I would say for in pediatric formulations as well as the experiment to development.

Ms. ESHOO. That is the debate on biosimilars but I didn't realize that it applied here.

Dr. KWEDER. Yes, it does in formulation development, yes.

Ms. ESHOO. Do you have any specific suggestions about how Congress can improve pediatric labeling?

Dr. KWEDER. Pediatric labeling? I think by some of the things in the BPCA that will allow us to link exclusivity to the scientific review process will result in better decisions on exclusivity and better decisions on labeling. I think otherwise we feel like we have most of the tools we need in pediatrics.

Ms. ESHOO. Thank you, Mr. Chairman. Thank you to the witnesses for your good work and your testimony.

Mr. PALLONE. Thank you. Mr. Murphy.

Mr. MURPHY. Thank you, Mr. Chairman. I would like to thank the panel. This is very enlightening. I want to further delve into something here that in terms of—Dr. Kweder, you are saying the program is working pretty well. My understanding is about 80 percent of the time the labeling of the drugs were changed to reflect the pediatric information obtained from this research. Does that number sound about correct?

Dr. KWEDER. That sounds about right.

Mr. MURPHY. OK. But among these drugs that show labeling changes, what percentage of the overall drugs the FDA has asked manufacturers to study does that reflect? So in other words, you may come up with 100 drugs. What percentage of those do the manufacturers really choose to study, to go into further?

Dr. KWEDER. I am not sure I am really understanding the question. I am sorry to be dense.

Mr. MURPHY. Let me explain then.

Dr. KWEDER. Yes.

Mr. MURPHY. Let us say you lay out 100 drugs that you would like some pediatric studies done on.

Dr. KWEDER. OK.

Mr. MURPHY. Do they do every one of those or do the companies decline sometimes?

Dr. KWEDER. Actually, we usually issue the written requests. Under the written requests we may ask for more studies than one, in fact, often we do.

Mr. MURPHY. What percent of the time will they do those?

Dr. KWEDER. Most of the time we have had overall, since the beginning of exclusivity which was actually 1997, we have had 41 companies decline to——

Mr. MURPHY. Why? Why did they decline?

Dr. KWEDER. They declined for a variety of reasons, sometimes because they are off-patent and they don't see a benefit.

Mr. MURPHY. What kind of benefit don't they see?

Dr. KWEDER. They see the pediatric market is too small to make it worth their while. They see that in order to address the written request, we have to ask for some of the basic scientific information that Dr. Mattison is referring to. They don't have the tools to address that.

Mr. MURPHY. So let me just continue on this. They say the pediatric population may be too small?

Dr. KWEDER. The pediatric population may be too small.

Mr. MURPHY. Too small for them to recover whatever investment and make the research based upon the 6-month exclusivity?

Dr. KWEDER. Yes, even with the 6-month exclusivity.

Mr. MURPHY. The 6-month thing doesn't give them enough?

Dr. KWEDER. It is not enough. And sometimes I don't have any exclusivity to attach to but we will ask them to do the study anyway. But there is no incentive. They are not going to do it.

Mr. MURPHY. And I want to clarify this because it is important. There are different kinds of populations of diseases, some are very common, unfortunately common and so companies may feel they can recoup their loss.

Dr. KWEDER. Right.

Mr. MURPHY. I am particularly concerned about some of the rare diseases of some children that I have treated myself and saw that no one was investing in some of these orphan diseases.

Dr. KWEDER. Right.

Mr. MURPHY. And are those the kind of things sometimes the companies say is just not worth their——

Dr. KWEDER. Yes.

Mr. MURPHY. I am really interested in any recommendations you have on how we correct this. Does the 6-month number work, and I don't know if all diseases should be treated equally here, and if some are more rare and have some awful tragic consequence but if we could somehow encourage companies to do some of the pediatric research on these, should we have different levels here? Some have 6 months, some have longer, so that they can look in terms of making the investments in some of these rarer diseases?

Dr. KWEDER. That is an interesting question. I am trying to remember. BPCA does apply to orphan products, but whether or not additional exclusivity would give companies the incentive to further their exploration of some of those even more orphaned pediatric indications as we do—some examples are things like juvenile rheumatoid arthritis, very, very rare. Doing pediatric studies is extremely difficult for a lot of these companies.

Mr. MURPHY. Yes.

Dr. KWEDER. If you are a large company particularly and you have some experience in doing trials in children, you have a setup system and you know how to do these, it is a very, very different kettle of fish than if you are a company that has just done adult studies, it takes an entirely different kind of expertise, entirely different network, and they just feel like they don't have the resources and the energy to even begin.

Mr. MURPHY. Exactly. Thank you so much for your comments on that because in my years of treating patients and psychologists, I remember one young man who was diagnosed with adrenal leukodystrophy, fairly rare, so much so that as I was identifying some of these symptoms, we had to search around for people who really knew these and treated these people.

Dr. KWEDER. Right.

Mr. MURPHY. And it was so tragic to watch this boy wither away because his body was basically eating away at itself in its own proteins and watch what happened as his own neurological development eroded. And yet I saw people were not really investing in treatments for someone like that. How many more diseases are there are like that? I hope that one of the things you might be able to provide this committee and send to the Chairman might be some ideas of how we deal with some other diseases because there are parents out there who feel that no one is paying attention to their

children and to treat all diseases as equal. I don't think it is fair to them, and I hope you can—I don't expect you to do it now but I hope that is something you can make some recommendations to the Chairman on.

Dr. KWEDER. No. Thank you.

Mr. MURPHY. Thank you, Mr. Chairman.

Mr. PALLONE. And we would certainly welcome those recommendations in writing. Thank you. Mrs. Capps.

Mrs. CAPPS. I also particularly appreciated this last exchange of questioning. It is has been lurking in the back of my mind, orphan diseases, adults or children but children in general are not a lucrative population for the topic that we are discussing today. How we can provide those services so that all patients can feel safe and confident that there is somebody looking out should something develop. I had two different questions to ask you since we have kind of jumped around here, Dr. Kweder. One is in the Best Pharmaceuticals for Children Act, HHS was required to issue a rule regarding the availability of a toll-free number which patients and providers could use to report adverse effects, and this rule was supposed to be proposed within 1-year of enactment. It is 3 years later, and I want to ask about that rule. Has it been released?

Dr. KWEDER. I am looking at my regulatory counsel here who is telling me that the answer is no.

Mrs. CAPPS. Well, you know what I am going to ask you next. When and why not?

Dr. KWEDER. We do have on all product labels, on all product labels, and we do require that the FDA MedWatch 1–800 number and Web site address be listed where anyone, healthcare provider or consumer, is encouraged to report any adverse effect related to any medicine. When one reports, one of the questions that is asked is what is the age of the patient, and so we are able to collect extensive amount of adverse event information through that system. We worked very hard over the years, now independent of this, to try and have one channel for communication to FDA so that people don't have to figure out, oh, did I call the right number? But that is one of the ways that FDA gets its information. One of the things that we have had to do in thinking about putting together this rule under BPCA is work through some consumer groups and do some testing to determine whether or not having a second number or second pathway is going to confuse things rather than help. And we are in the process of completing some of those studies.

Mrs. CAPPS. In this case it would be parents most likely who would be reporting because of the——

Dr. KWEDER. That is right. And that is typically how we get the information, even through our MedWatch system about children from—the children don't report them themselves obviously, the parents do.

Mrs. CAPPS. And I think again with all the questions that have come up with what we are talking about, this is so important for us to know, for you all to know, and the public to feel confident that this unique population, always changing, developing, is going to be acknowledged in terms of any kind of effect, good, bad, or——

Dr. KWEDER. Right. And this kind of information is exactly the kind of information that we ask our Pediatric Advisory Committee

to review at the 1-year mark, information about both adults and children, after exclusivity is granted.

Mrs. CAPPS. Now, a different topic but also based on child development. Children, because they are constantly growing and developing, it is even more important I believe that ongoing clinical studies are part of that process to determine the long-term safety and efficacy of either a device or a pharmaceutical. But currently there is a 3-year limit on FDA mandated post-market studies on medical devices. An Institute of Medicine report released in 2005 recommends that this 3-year limit be lifted because it restricts the FDA from mandating appropriate studies involving devices effects on children growth and development. I wonder if you agree with this conclusion and the suggestion that this limit should happen, be lifted. And Dr. Less? OK.

Ms. LESS. Congresswoman Capps, thank you very much. Before I answer your question, let me just say thank you to Chairman Pallone and the members of the subcommittee for inviting us today to speak with you on this important issue, both post-market safety of pediatric medical devices as well as facilitating the development of new devices. We welcome this opportunity and look forward to working with you this very important issue.

With regard to section 522, currently it is limited to 3 years, and we agree with the IOM that in some cases, especially in the cases of implants, it would be important to be able to go longer than the 3 years. Right now, if we want to go longer we have to work with the manufacturer and get their agreement in order to do so. We have not had that problem or we think that because manufacturers are paying much more attention and recognize the importance of collecting this information, it hasn't been an issue. But we would not be opposed to having that additional authority.

Mrs. CAPPS. Good. I was just thinking of an important or some device for a 2-year-old would not—at 3 years, they are still very much in the process of developing. So I would hope that this advise be taken seriously in the reauthorization.

Ms. LESS. Thank you.

Mr. PALLONE. Thank you. Mr. Green.

Mr. GREEN. Dr. Mattison, would you like to explore the requirements of NIH and the resources it receives to study the drugs both on-patient and off-patient, and can you compare the process and resources NIH receives distinguishing between the off-patent and on-patent drugs, resources comparison.

Dr. MATTISON. The funding that we use to support the studies that we do on the drugs comes from contributions from the 19 institutes and centers that are participating with us in the BPCA activities, and those cover the studies that we need to conduct both on- and off-patent drugs. We also receive contributions from the foundation for the NIH to help defray the cost of the on-patent drug studies that we are engaged in, but those contributions are substantially less than the cost of the studies themselves.

Mr. GREEN. Do you have any comparison of the process or resources it receives? That is the only funding you receive?

Dr. MATTISON. I am sorry. I am not sure I understand it, but the funding from the institutes has been a set contribution from each of them since 2004. Again, through the foundation for the NIH,

they have provided us what they felt was appropriate based on the resources that they have collected. I am sorry if I am not answering you.

Mr. GREEN. Are there any private contributions?

Dr. MATTISON. There are private contributions that come to the foundation for the NIH. I can't answer the question about who has contributed those.

Mr. GREEN. OK. Recently a published GAO report on studies conducted under the BPCA had noted that the process for approving labeling changes is often lengthy for drugs that have labeling changes after being granted exclusivity. The report states that it took between 238 and 1,055 days for information to be reviewed and labeling changes to be approved for approximately 40 percent of the drugs granted exclusivity, with seven of these taking more than a year. Drug studies under the BPCA are used for a number of life-threatening diseases. Would you agree that the amount of time consumed for labeling changes to occur poses a dangerous public health concern for some children and why is it taking so long for labeling changes to occur? Is it lack of resources?

Dr. MATTISON. That I think is a question for the FDA.

Dr. KWEDER. I would be happy to answer that question. When we make an approval for labeling changes, it is usually based on a scientific review which as I mentioned before is on a different time clock than the exclusivity determination. So the exclusivity determination precedes the ultimate decision on how and whether to label a product. Decisions about labeling ultimately depend on the scientific data available that underlie those changes. For a priority application, we would usually render a decision on that scientific application at 6 months, others are a 10-month clock. It is not unusual for us to have to go back and ask for more information and another round of review before we can have the confidence that we need in the labeling that we want to make. We have become I would say since we started these programs a few years ago much better at getting those out there more quickly and making cuts on labeling changes that we can make early while we wait for additional data to supplement the labeling later. But there will always be a situation where we are stuck with needing more information before we can make a confident change to a label.

Mr. GREEN. But it is not from lack of resources?

Dr. KWEDER. No.

Mr. GREEN. What about with disagreements with manufacturers on labeling?

Dr. KWEDER. Again, that is an area where we have been really pushing the envelope to getting these things into the label. We feel very strongly that information about pediatric use of products needs to be available to practicing clinicians. Our best tool for that is the labeling. We do have a provision in the statutes that allows us to take a labeling dispute with a company to the Pediatric Advisory Committee. We have not had to utilize that to date.

Mr. GREEN. So you are saying that the numbers I gave, you know, the 238 to 1,055 days, it is much better in the last few years?

Dr. KWEDER. Yes, yes. Absolutely.

Mr. GREEN. OK. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you. The gentlewoman from Illinois?

Ms. SCHAKOWSKY. Thank you, Mr. Chairman. I am picking up a little bit on what Mr. Waxman had raised about the cost of actually doing the pediatric studies versus the amount of money that the pharmaceutical companies make with this exclusivity provision. The Wall Street Journal estimated that pediatric studies have grown from $200,000 to $3 million each. Does that sound right or is that $200,000 maybe a little low?

Dr. MATTISON. $200,000 is awfully low.

Ms. SCHAKOWSKY. OK.

Dr. MATTISON. The studies that we are conducting, depending upon the severity of the disease and the children that are enrolled in the study, they typically cost in the $10 to $15 million range.

Ms. SCHAKOWSKY. OK. And yet, 6 months of additional exclusivity was worth nearly $8 billion for Prozac and $575 million for Claritin. So regardless, $10 or $15 million, it is a lot of money, potentially a lot of money in exclusivity. My staff is telling me that the FDA has estimated that consumers will pay nearly $14 billion in higher prescription drug costs over the next 20 years if the current pediatric exclusivity program is reauthorized. You look quizzical. Is that——

Dr. KWEDER. That is not a statistic I am familiar with.

Ms. SCHAKOWSKY. OK. Maybe my staff will write me a note while I am asking the rest of the questions. And I am concerned though that these high prices and the differential is so high, is virtually borne by senior citizens who are the highest consumers of and have a disproportionate share of prescription drug use and the uninsured who have to pay the full cost. And I am concerned that under the current system of granting additional exclusivity, there really is little incentive for companies to test drugs other than the blockbusters.

For example, I have Glucophage, a diabetes medication, received an exclusivity period worth about $640 million, yet it is barely used for children. Less than one percent of its prescriptions are written by pediatricians. And six out of the 10 drugs most widely used in children without adequate labeling are not eligible for pediatric exclusivity because they are already off-patent. So should we be considering this differential and how much it is worth to the drug companies because ultimately the consumers pay the cost and how can we incentivize studies in these very important drugs? I mean, if the companies can simply decline to do the studies, then as Mr. Green was exploring, that money then is entirely borne by the taxpayers. Are these issues that we need to deal with? In my opinion I think they are. So either or both of you actually——

Dr. KWEDER. I will take a stab. These are really difficult issues. One of the things that we do when we have a company that declines an initial written request, to go to your last point first, sometimes there is a long period of time that passes that they have been thinking about that and events occur in the interim that make that written request— for example, we look very carefully to make sure that this is something that we want the taxpayers to really fund. Sometimes new information has come to light while they were thinking about that written request that changes the public health value equation. So we would make a decision to put that lower on

the priority list for NIH funding. The struggle that the public has in assessing value is looking at the cost of studies, the financial gain that companies receive in terms of exclusivity, the cost to the public of generic drugs, those are all factors I have to say the monetary costs have not really been part of the equation for FDA in deciding what to ask for in the way of studies. We have really based our decisions on seeking study data on what we perceive to be a potentially important public health benefit.

To use the example of the Glucophage that you raised, that is one of the oldest oral diabetic agents on the market; and while the population of pediatric users today may be small, we have an epidemic of obesity in pediatric population that is growing in this county. In particular in Type II diabetes, the type that is associated with obesity, that is a mainstay of therapy among diabetics. So we expect that physicians are going to increasingly be seeking to use those kinds of treatments in children. So it was very important we felt from a public health standpoint to really understand whether that drug was safe in children and whether it was effective. We learned that it is not effective in children. That is an enormously important public health benefit and prevents children from being exposed to a drug that is not effective and may only have risks. I don't know how we could attach a monetary value to this, and that has been our struggle in thinking about how to assign different values in terms of——

Ms. SCHAKOWSKY. But clearly the companies are assigning a monetary value when they decline to do a study.

Dr. KWEDER. Yes, they are.

Ms. SCHAKOWSKY. I am not trying to put a price tag on the life of a child but there certainly is a cost benefit analysis and it is pretty easy for the companies to say, well, it is off-patent, we decline.

Dr. KWEDER. Yes.

Ms. SCHAKOWSKY. I wondered if you had any comment doctor, even though I am out of time, Mr. Chairman. Can I ask him if he has any comments?

Mr. PALLONE. We will ask Dr. Mattison and then we will move on.

Dr. MATTISON. Again, we focus our attention on the off-patent drugs because we assume that those will get the least attention by any other interested group, and we feel that by focusing our attention on that group of drugs and identifying those that provide the greatest public health benefit in terms of what do we know versus what would we like to know to improve those drugs, we at the NIH can make the best impact possible under BPCA.

Ms. SCHAKOWSKY. Thank you. Thank you, Mr. Chairman.

Mr. PALLONE. Thank you and I thank all three of you for your input in answering our questions, and I think as you know you may get additional questions from us within the next 10 days or so; and please follow through. Thank you.

Dr. KWEDER. We will, and thank you very much.

Mr. PALLONE. And if the next panel could come forward and I ask that the panel be seated.

Let me start by introducing each of you. On my left is Ms. Lori Reilly who is vice president for policy and research for PhRMA; and

then we have Dr. Marcia Crosse who is director of health care issues for the GAO; and then we have Dr. Gorman, Richard Gorman, who is chair of the AAP section on Clinical Pharmacology and Therapeutics for the American Academy of Pediatrics; we have Dr. Peter Lurie who is deputy director of Public Citizen's Health Research Group; we have Ms. Susan Belfiore who is testifying on behalf of Elizabeth Glaser Pediatric AIDS Foundation; we have Mr. Ed Rozynski who is vice president for Global Government Affairs at Stryker Corporation; and last is Mr. Donald Lombardi who is president and CEO of the Institute for Pediatric Innovation.

We are going to give each of you 5 minutes. You can, of course, submit additional written statements if you like with the committee's permission afterwards; and we will start with Ms. Reilly. Thank you.

STATEMENT OF LORI REILLY, VICE PRESIDENT, POLICY AND RESEARCH, PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA

Ms. REILLY. Thank you Chairman Pallone and members of the subcommittee for having me here today. My name is Lori Reilly, and I am vice president for policy and research at the Pharmaceutical Research and Manufacturers of America, otherwise known as PhRMA.

I have seen firsthand the benefits of this program. While I am here today in my capacity representing PhRMA, I am also a mother; and I have seen the benefits firsthand of this program. When my youngest daughter was born, at about 6 weeks of age my husband noticed that she had a strange, wheezing sound when she was breathing. Obviously this is alarming as a parent to hear that and we were worried about whether she was getting enough air and whether she had the ability to breathe correctly. After seeing our pediatrician and a pulmonologist and an ear, nose, and throat specialist, she was diagnosed with a rare condition called laryngomalacia which is a fancy term for a floppy voice box which thankfully self-corrects itself in about 18 months. One of the other symptoms in addition to having trouble breathing is significant reflux or vomiting and this was causing a problem because she was having an inability to gain weight. Thankfully there was a drug available that was approved under BPCA that allowed my pediatrician to prescribe the drug to her that controlled that symptom and also allowed her to gain weight. So I thank Congress personally for enacting these very important provisions because I am not unlike many other parents in this country and families that have seen firsthand the benefits of this program.

As the FDA has said, the current pediatric exclusivity program has done more to further research and generate clinical information for pediatric populations, and it is a very important program. By the end of 2006 alone, FDA had issued nearly 400 written requests for almost 800 studies to be done on pediatric patients. In comparison, when you look back prior to the enactment of this program, from 1990 to 1997, only 11 drugs had been studied in children. So clearly we have made a lot of progress in a short period of time.

Companies are responding to written requests from FDA in very high numbers. Back in 2001, FDA had estimated that about 80 percent of the time companies would respond proactively to a written request; and in fact, they are doing that anywhere from 81 to 84 percent of the time depending on the data that you look at. And not only are companies responding in high amounts, they are also responding to broad categories of disease. According to the GAO, about 17 broad categories of disease including cancer, which is obviously a very significant condition, was the most studied condition under the pediatric exclusivity program.

In less than 10 years since the program began, over 120 drugs and conditions have had new labeling changes as a result of this program, and in fact nearly 90 percent of all drugs that have been granted exclusivity under BPCA have received important labeling changes. And this is important because when we look at, for example, a study that was done in JAMA and you look at the time period between 2002 and 2004, there were 59 drug products that received exclusivity under BPCA. And prior to 2002, about 34 percent of those drugs had been used and physicians were prescribing these drugs, either making a dosing error or placing a child at risk of serious adverse events. So having this critical information available to patients and doctors is vitally important.

While the benefit of this program has continued to grow over time since its inception, also growing are the cost, time, and complexity to do these studies. Companies have continued, however, in engaging in this research despite the increase in time and costs. From 2000 to 2006, the average number of patients per written request increased 178 percent while the average number of studies requested by the FDA in a written request increased by 60 percent. Sponsors have also been increasing the proportion of the safety and efficacy tests, often the most expensive and time-consuming of all tests done by companies from 25 percent in 2000 to 40 percent in 2006. The time required to complete pediatric studies has also increased significantly. It has doubled in fact in the last 6 years. And the average cost to complete a written request has increased eightfold. Given these significant increases we have seen in the cost, time, scope, and complexity of studies, it is PhRMA's position that Congress should not adopt significant modifications to these programs that may inevitably reduce incentives for companies to engage in this kind of research. As we know, these provisions have had a tremendously positive impact on the lives of children, but there is much more to be accomplished. The program is working well, and its basic features should not be altered. Changes in the current program have the potential to reduce incentives that exist for companies to engage in this very important research.

As mentioned above, the cost, time, and complexity of these studies is increasing. Given these factors, Congress should not increase the hurdle that companies must go through to qualify for pediatric exclusivity. As I mentioned earlier in my testimony, companies have pursued pediatric studies for a broad range of conditions, about 17 in total; but the majority of drugs studied under these programs were not high-selling drugs, nor were they blockbuster drugs. In fact, 60 percent of the drugs studied were not even in the top 200 selling drugs. Some of these drugs included medicines for

HIV/AIDS, leukemia, anti-infectives and others. Again, only about 10 percent of the drugs studied under this program are what you would consider blockbuster drugs.

As with drug development in general, blockbuster drugs and higher-revenue drugs, support the ability of pharmaceutical companies to invest in research for lower-selling, lower-volume drugs. And in the case of pediatrics, not only have blockbusters allowed companies to invest in research for lower volume or lower-selling drugs and clearly companies are, it has also given the companies the ability to build needed infrastructure for pediatric programs. This infrastructure includes hiring researchers that have particular expertise in pediatric populations and building the kind of in-house infrastructure needed. Unique expertise is required to develop drugs for use in children, and thanks to the pediatric incentive, companies have made significant investments in building capabilities in this area.

We must preserve the pediatric exclusivity as it is currently structured to ensure that pediatric drug development is not hindered. Diminishing or reducing the value of incentives, for instance, by reducing the exclusivity period or tiering it for certain products could also create unintended consequences throughout the program. In addition, BPCA and PREA are complimentary programs and should remain connected as they have to date. Together these two programs have worked extremely well to generate new information on pediatric use.

In conclusion, PhRMA strongly urges Congress to reauthorize BPCA and PREA without modification. The increasing rate of industry study proposals and FDA written requests shows continuing progress which could be significantly undermined of these two programs 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. Thank you.

[The prepared statement of Ms. Reilly follows:]

Lori M. Reilly
Vice President, Policy & Research
Pharmaceutical Research and Manufacturers of America

Before the
House Committee on Energy and Commerce
Subcommittee on Health
"Programs Affecting Safety and Innovation in Pediatric Therapies"
May 22, 2007

Mr. Chairman, Rep. Deal, and Members of the Subcommittee:

Thank you for the invitation to participate in today's hearing on programs affecting safety and innovation in pediatric therapies. My name is Lori Reilly and I am the Vice President for Policy and Research at the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA is the nation's leading trade association representing research-based pharmaceutical and biotechnology companies that are devoted to inventing new, life-saving medicines.

In sum, my testimony today will highlight the following points:

- The current pediatric exclusivity program has been extraordinarily successful in improving medical care for children. According to the Food and Drug Administration (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.
- Far more pediatric studies have been conducted over the last 10 years, since pediatric exclusivity was created, than in all the pre-exclusivity years combined. These studies are widely recognized as having yielded

extensive and vitally important information about how medicines can best be used in the treatment of children.

- According to the U.S. Government Accountability Office (GAO), the most frequently studied drugs were those to treat cancer, neurological and psychiatric disorders, metabolic diseases, cardiovascular disease, and viral infections.
- 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.
- From 2000 to 2006, the scope of pediatric studies has expanded significantly. The average number of studies and patients per written request have increased dramatically, as has the share of programs required to perform long-term follow-up studies.
- The cumulative number of pediatric studies completed since 1998 rose from 58 at the end of 2000 to 568 at the end of 2006.
- Despite the incentive the pediatric exclusivity program has provided, pediatric studies are done at risk. Even when a company is granted exclusivity, the value of such exclusivity may be diminished (or nullified) due to other factors.
- Less than half of the products that received pediatric exclusivity were in the top 200 selling drugs. Only about one-tenth of drugs awarded pediatric exclusivity were in the "blockbuster" category.

- 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. GAO, the Senate Health, Education, Labor and Pensions (HELP) Committee, and practitioners have recognized that the current pediatric exclusivity incentive has done much to expand this valuable infrastructure for pediatric drug programs.
- In light of these facts, the current program should be reauthorized. The incentive should not be reduced, for example by reducing the exclusivity period or by tiering exclusivity for certain drug products.

History of Pediatric Exclusivity Program

Historically in the U.S., 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 Administration 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 FDA.

[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.

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 an additional six-month period of exclusivity, known as 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 pediatric exclusivity period begins on the date that the existing patent or marketing 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 Best Pharmaceuticals for Children Act (BPCA) in 2002. The BPCA sunsets on October 1, 2007, unless reauthorized.

Under the BPCA, the FDA can issue requests for pediatric studies of both approved and unapproved 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. 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 because these products have no remaining patent or marketing exclusivity periods.

In addition to the BPCA, the Pediatric Research Equity Act (PREA) gives FDA the authority to require studies of drugs for the approved 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 could pose significant risks 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 or 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

[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.

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 information 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 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

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[5] "Pediatric Drug Research: Studies Conducted under Best Pharmaceuticals for Children Act," GAO-07-557 (March 2007), at 5.
[6] Id. at 21.
[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.*

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 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 concerning the use of products in children 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] According to the *JAMA* study, data for 59 products were submitted to the FDA between 2002-2004. Using the numbers from the labeling information for these 59 drugs, the study found that 34 percent of the time that physicians prescribed the drugs from this cohort before 2002, they were making a dosing error or placing a child at risk of adverse events with limited therapeutic benefit. As the article stated, "Administration of safe drugs that work, at an appropriate dosage, is critical to public health."[13] Similarly, the Elizabeth Glaser Pediatric AIDS Foundation has stated, "the [pediatric

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[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] Li et al., "Economic Returns of Clinical Trials Performed Under the Pediatric Exclusivity Program," JAMA, February 7, 2007, Vol. 297, No. 5.

exclusivity] incentives are proven to deliver life-saving information for children – the same information that we expect and demand for ourselves as adults."[14]

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, fortunately, 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

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

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 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, and could include different dosage forms for each of these drugs.

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.

Companies Continue Responding to the Incentive as Complexity and Cost of Pediatric Studies Increase

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. At the same time, companies have continued 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.[15] This conclusion is supported by the Tufts Center, which found an 84 percent industry response rate to FDA written requests for pediatric studies.[16] 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, while the average number of studies per written request rose 60 percent.[17] There was also a doubling of the share of programs required to perform long-term follow-up studies (from 17 percent to 33 percent).[18]

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.[19] In addition to time, the average cost to respond to a written request increased 8-fold from 2000 to 2006.

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

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[15] Pediatric Drug Research: Studies Conducted under Best Pharmaceuticals for Children Act, GAO-07-557 (March 2007).
[16] 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.
[17] Id.
[18] Id.
[19] Id.

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 currently unapproved indications, while 40 percent were for already approved indications.[20]

The Pediatric Exclusivity Incentive Should Remain Intact

The pediatric exclusivity incentive has had a tremendous positive impact on the lives of children, but there is much more to be accomplished. For this reason, the current program – which is working well-- and its basic features should 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 addition, even when a company is granted exclusivity, the value of such exclusivity may be diminished (or nullified) due to other factors. 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

[20] Id.

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 the incentive's value, or even if that it will remain available at the time all existing patent protection and marketing exclusivity expires. Given these factors, Congress should not increase the hurdles necessary to qualify for pediatric exclusivity.

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.[21] 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.[22]

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

[21] 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.
[22] Id.

ability to build pediatric programs and infrastructure over the past decade. Prior to enactment of the pediatric exclusivity incentive, such infrastructure did not exist. It is very important to understand that without this infrastructure, which needs to be permanent, it could impact companies' ability to conduct pediatric drug development. Unique expertise is required to develop drugs for use in children, and thanks to the pediatric incentive, companies have made significant investments in building capabilities in this area. As such, maintaining the current incentive structure will be critical to continued research in this area.

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."[23] 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."[24] 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."[25]

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

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[23] "Drug Research and Children," FDA Consumer (January – February 2003), http://www.fda.gov/fdac/features/2003/103_drugs.html
[24] 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.
[25] S. Rep. No. 107-79 (October 4, 2001).

are allocated across drug portfolios...these medicines indeed provide the fuel to drive research and development of less remunerative compounds..."[26] 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."[27]

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."[28]

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, for instance by reducing the exclusivity period or by tiering exclusivity for certain drug products could also create unintended ripple effects across the entire program. While some have argued the returns received from some products (namely blockbuster drugs) 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. Specifically on the issue of proposals to institute a tiered exclusivity incentive, this structure fails to recognize the basic structure of the pharmaceutical research sector, in which a few high-selling medicines often support the

[26] Id.
[27] Id.
[28] S. Rep. No. 107-79, October 4, 2001.

research investment in medicines that are needed but that do not achieve large sales. In fact, research conducted by economists at Duke University found that on average, 7 out of every 10 approved medicines do not recover their average development cost. The authors concluded that companies must rely on a limited number of highly successful products to finance their continuing R&D.[29]

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.

BPCA and PREA are Complimentary Programs that Should Remain Connected

BPCA and PREA are complimentary programs that should remain connected. PhRMA would propose eliminating the sunset for both programs or alternatively sunsetting them at the same time. It could be very damaging to the operation of companies pediatric research programs if one program continues without the other. As discussed previously, the pediatric exclusivity provisions have been an overwhelming success, generating more than 120 new pieces of information in drug labeling. At the same time, the pediatric assessment provisions in section 505B of the FDCA have generated new labeling in 63 drug products, according to a recent CRS report. Together, these two programs have worked extremely well to generate new information on pediatric uses of drug products, and they should remain linked. In the past, Congress made certain that the PREA study authority remained in effect so long

[29] Grabowski H. and Vernon J., "Returns to R&D on New Drug Introductions in the 1980s," Journal of Health Economics, Vol. 13, 1994.

as the pediatric exclusivity incentives also remain in effect. This ensured that the two programs were tied together, and evaluated together. This is the right approach. Given the success of the programs and the complimentary nature of each to the other, there is simply no reason why the two programs should be de-linked. Accordingly, we urge Congress to adopt a mechanism that allows both to be both made permanent or both re-examined in 2012.

Conclusion

PhRMA strongly urges Congress to reauthorize the BPCA and PREA without modification. 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.

Mr. PALLONE. Dr. Crosse.

STATEMENT OF MARCIA CROSSE, DIRECTOR, HEALTH CARE ISSUES, U.S. GOVERNMENT ACCOUNTABILITY OFFICE

Ms. CROSSE. Mr. Chairman and members of the subcommittee, I am pleased to be here today as you examine pediatric therapies. My remarks are based on GAO's recent report on the Best Pharmaceuticals for Children Act, BPCA. I will focus on studies conducted under BPCA for on-patent drugs, for off-patent drugs, and the impact of the statute on the labeling of drugs for pediatric use. As we have heard here today, when FDA determines that a drug may provide health benefits to children, it may issue a written request of the drug sponsor to conduct pediatric drug studies. A drug sponsor can also propose to FDA that a written request be issued for a particular drug, but FDA makes the determination of whether this is warranted. Only a minority of the studies that sponsors proposed resulted in FDA issuing a written request.

BPCA has been relatively successful in promoting the study of on-patent drugs. Drug sponsors agreed to study over 80 percent of the on-patent drugs for which FDA issued written requests. Studies have been completed for about one-third of these drugs. Of those drug studies completed and submitted to FDA, over 90 percent have resulted in FDA granting pediatric exclusivity. A total of 73 drugs to date under BPCA and 136 drugs under BPCA and its predecessor, FDAMA. FDA grants exclusivity regardless of whether the studies show the drug should be used to treat children. Indeed a finding that a drug should not be used in children can be just as valuable as a finding that shows positive results.

In contrast to the relative success of the process when drug sponsors agree to conduct the requested studies, the picture is much less positive when the drug sponsor declines. To date, the study of only one on-patent drug has been initiated when the drug sponsor declined the written request. BPCA allows FDA to refer declined written requests for on-patent drugs to the Foundation for the National Institutes of Health, FNIH, an independent, non-profit corporation that raises private sector funds for research including for BPCA studies. Through 2005, drug sponsors declined 41 written requests for on-patent drugs and FDA chose to refer nine of these to FNIH for funding. FNIH subsequently agreed to fund the study of one of these drugs, even though all its available funding for BPCA studies could only provide partial support for this research. As of June 2006, FNIH had only raised about $4 million to fund BPCA studies, and the study of this one drug was estimated to cost about $8 million. Similarly, few off-patent drugs have been studied under BPCA. Through 2005, NIH had identified 40 off-patent drugs it recommended for study and FDA issued written requests for 16 of these drugs. However, drug sponsors declined 15 of these 16 written requests. NIH subsequently used its appropriations to fund studies for half of these off-patent drugs. Under BPCA the most frequently studied drugs were those used to treat cancer, neurological and psychiatric disorders, metabolic diseases, cardiovascular disease, and viral infections. In addition, about half of the 10 drugs most frequently prescribed for children have been studied under BPCA. Moreover, almost 90 percent of the drugs that have been

granted pediatric exclusivity have had important labeling changes, but the process for reviewing the study results and making these changes can be lengthy. The labeling of drugs was often changed because pediatric drug studies revealed that children may have been exposed to ineffective drugs, ineffective dosing, overdosing, or previously unknown side-effects. For the drugs we examined, they took between 238 and 1,055 days or almost 3 years for FDA to approve the labeling changes when the agency required additional information to support the proposed changes.

In conclusion, BPCA has made important contributions to increasing the knowledge of appropriate usage of drugs in children. The drugs studied under the statute are used to treat children for a broad range of diseases and many serious or life-threatening conditions. However, the provisions to promote the study of a drug when the sponsor declines the written request or when a drug is off-patent have worked less well. Funding has not been sufficient to ensure that in these situations studies of the drugs are undertaken.

Mr. Chairman, this concludes my prepared remarks. I would be happy to respond to question that you or other members of the subcommittee may have.

[The prepared statement of Ms. Crosse follows:]

United States Government Accountability Office

GAO

Testimony
Before the Subcommittee on Health, Committee on Energy and Commerce, House of Representatives

For Release on Delivery
Expected at 10:00 a.m. EDT
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PEDIATRIC DRUG RESEARCH

The Study and Labeling of Drugs for Pediatric Use under the Best Pharmaceuticals for Children Act

Statement of Marcia Crosse
Director, Health Care

GAO-07-898T

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Highlights

Highlights of GAO-07-898T, a testimony before the Subcommittee on Health, Committee on Energy and Commerce, House of Representatives

Why GAO Did This Study

About two-thirds of drugs that are prescribed for children have not been studied and labeled for pediatric use, placing children at risk of being exposed to ineffective treatment or incorrect dosing. The Best Pharmaceuticals for Children Act (BPCA), enacted in 2002, encourages the manufacturers, or sponsors, of drugs that still have marketing exclusivity—that is, are on-patent—to conduct pediatric drug studies, as requested by the Food and Drug Administration (FDA). If they do so, FDA may extend for 6 months the period during which no equivalent generic drugs can be marketed. This is referred to as pediatric exclusivity. BPCA also provides for the study of off-patent drugs.

GAO was asked to testify on the study and labeling of drugs for pediatric use under BPCA. This testimony is based on *Pediatric Drug Research: Studies Conducted under Best Pharmaceuticals for Children Act*, GAO-07-557 (Mar. 22, 2007). GAO assessed (1) the extent to which pediatric drug studies were being conducted under BPCA for on-patent drugs, (2) the extent to which pediatric drug studies were being conducted under BPCA for off-patent drugs, and (3) the impact of BPCA on the labeling of drugs for pediatric use and the process by which the labeling was changed. GAO examined data about the drugs for which FDA requested studies under BPCA from 2002 through 2005 and interviewed relevant federal officials.

www.gao.gov/cgi-bin/getrpt?GAO-07-898T.

To view the full product, including the scope and methodology, click on the link above. For more information, contact Marcia Crosse at (202) 512-7119 or crossem@gao.gov.

May 22, 2007

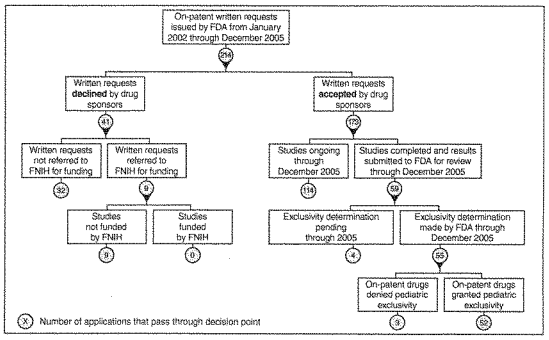
PEDIATRIC DRUG RESEARCH

The Study and Labeling of Drugs for Pediatric Use under the Best Pharmaceuticals for Children Act

What GAO Found

Drug sponsors have initiated pediatric drug studies for most of the on-patent drugs for which FDA has requested such studies under BPCA, but no drugs were studied when sponsors declined these requests. Sponsors agreed to 173 of the 214 written requests for pediatric studies of on-patent drugs. In cases where drug sponsors decline to study the drugs, BPCA provides for FDA to refer the study of these drugs to the Foundation for the National Institutes of Health (FNIH), a nonprofit corporation. FNIH had not funded studies for any of the nine drugs that FDA referred as of December 2005.

Written Requests Issued under BPCA for the Study of On-Patent Drugs (2002-2005)



Source: GAO.

Few off-patent drugs identified by the National Institutes of Health (NIH) that need to be studied for pediatric use have been studied. BPCA provides for NIH to fund studies when drug sponsors decline written requests for off-patent drugs. While 40 such off-patent drugs were identified by 2005, FDA had issued written requests for 16. One written request was accepted by the drug sponsor. Of the remaining 15, NIH funded studies for 7 through December 2005.

Most drugs granted pediatric exclusivity under BPCA (about 87 percent) had labeling changes—often because the pediatric drug studies found that children may have been exposed to ineffective drugs, ineffective dosing, overdosing, or previously unknown side effects. However, the process for approving labeling changes was often lengthy. For 18 drugs that required labeling changes (about 40 percent), it took from 238 to 1,055 days for information to be reviewed and labeling changes to be approved.

Mr. Chairman and Members of the Subcommittee:

Although children suffer from many of the same diseases as adults and are often treated with the same drugs, only about one-third of the drugs that are prescribed for children have been studied and labeled for pediatric use.[1] This has placed children taking drugs for which there have not been adequate pediatric drug studies at risk of being exposed to ineffective treatment or receiving incorrect dosing. In order to encourage the study of more drugs for pediatric use,[2] Congress passed the Best Pharmaceuticals for Children Act (BPCA) in 2002 to provide marketing incentives to drug sponsors for conducting pediatric drug studies.[3] Drug sponsors (typically drug manufacturers) may obtain 6 months of additional market exclusivity for drugs on which they have conducted pediatric studies in accordance with pertinent law and regulations.[4] This market exclusivity is known as pediatric exclusivity. When a drug has market exclusivity, it is protected from competition for a limited period; for example, the Food and Drug Administration (FDA) is prohibited from approving a generic copy for marketing.[5] Generally, pediatric exclusivity can only be granted to those drugs that are on-patent—that is, those that still have market

[1]The drug "label" refers to written, printed, or graphic material placed on the drug container while drug "labeling" is much broader and includes all labels and other written, printed, or graphic materials on any container, wrapper, or materials accompanying the drug. 21 U.S.C. § 321(k), (m).

[2]FDA generally defines the pediatric population covered under BPCA as children from birth to 16 years old, though studies have included children as old as 18.

[3]Provisions regarding pediatric studies of drugs are generally codified at 21 U.S.C. § 355a. Pub. L. No. 107-109, 115 Stat. 1408. The market exclusivity provisions of BPCA will sunset on October 1, 2007.

[4]The value of 6 months additional marketing exclusivity is difficult to assess and depends on a number of factors for which data are not available. However, a recent study estimated that for some drugs, the benefit of 6 months of marketing exclusivity was quite large, while for others the return the drug sponsor received for pediatric exclusivity was less than the cost of the studies. See Jennifer S. Li, et al., "Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program," *JAMA*, vol. 297, no. 5 (2007).

[5]Drug sponsors can obtain additional market exclusivity or patent protection for drugs protected by patents, drugs designed to treat rare diseases, drugs consisting of new chemical entities, and already-marketed drugs approved for new uses. *See, for example*, 21 U.S.C. §§ 355(j)(5)(F)(ii), (iii); 21 C.F.R. § 314.108 (2006). Pediatric exclusivity under BPCA attaches to an existing listed patent or any existing market exclusivity held by the drug sponsor.

exclusivity[6]—and for which FDA has issued a written request for pediatric drug studies.[7] However, FDA can also request pediatric drug studies for off-patent drugs—drugs for which the patent or market exclusivity has expired. BPCA also included provisions designed to provide for the study of both on-patent and off-patent drugs that drug sponsors have declined to study.

When FDA determines that a drug may provide health benefits to children, it may issue a written request to the drug sponsor to conduct pediatric drug studies on that drug. When a drug sponsor accepts a written request and conducts studies, FDA reviews the report from the pediatric drug studies to determine whether to grant pediatric exclusivity to the drug. If FDA is satisfied that the studies have been conducted and reported properly, the drug in question may receive additional market exclusivity. FDA also reviews these pediatric drug study reports to see if the drug requires labeling changes.

BPCA provides for pediatric drug studies when the drug sponsor declines the written request. First, if a drug sponsor declines a written request from FDA to study an on-patent drug, BPCA provides for FDA to refer the drug to the Foundation for the National Institutes of Health (FNIH), which can fund the study if funds are available.[8] Sponsors cannot receive pediatric exclusivity for on-patent drugs that drug sponsors decline to study. Second, BPCA provides for the funding of the study of off-patent drugs by the National Institutes of Health (NIH), which, in consultation with FDA and experts in pediatric research, identifies off-patent drugs that need to be studied for pediatric use.

My remarks today provide an overview of the study and proper labeling of drugs for pediatric use under BPCA. I will focus on (1) the extent to which pediatric drug studies were being conducted under BPCA for on-patent drugs, (2) the extent to which pediatric drug studies were being conducted

[6]For purposes of this statement, we refer to drugs that have patent protection or market exclusivity as on-patent and those whose patent protection or marketing exclusivity has ended as off-patent. This is the same terminology typically used by government agencies to describe the exclusivity status of a drug under BPCA.

[7]FDA is responsible for issuing written requests for pediatric studies, determining whether a drug merits pediatric exclusivity as a result of those studies, and all steps in between.

[8]FNIH is an independent, nonprofit corporation. The majority of funds that FNIH receives are from the private sector. Only a portion of these funds are available for FNIH to award to researchers to conduct studies related to BPCA.

under BPCA for off-patent drugs, and (3) the impact of BPCA on the labeling of drugs for pediatric use and the process by which the labeling was changed. My remarks are based upon our report assessing the effect of BPCA on pediatric drug studies and labeling.[9]

In carrying out the work for our report, we collected and analyzed a variety of data from FDA, NIH, and FNIH about written requests and pediatric studies for both on- and off-patent drugs from January 2002 through December 2005. Our work focused on actions regarding these drugs prior to 2006. To evaluate the impact of BPCA on the labeling of drugs for pediatric use and the process by which labeling was changed, we reviewed summaries of the labeling changes for drugs studied from the enactment of BPCA through 2005. In addition, to assist with our review in general, we interviewed officials from FDA, NIH, and FNIH. The work done for this statement was performed from September 2005 through March 2007 in accordance with generally accepted government auditing standards.

In summary, most of the on-patent drugs for which FDA requested pediatric drug studies under BPCA were being studied, but no studies resulted when the requests were declined by drug sponsors. Drug sponsors agreed to study 173 of the 214 on-patent drugs (81 percent) for which FDA issued written requests for pediatric drug studies from January 2002 through December 2005. Drug sponsors completed pediatric drug studies for 59 of the 173 accepted written requests—studies for the remaining 114 written requests were ongoing—and FDA made a pediatric exclusivity determination for 55 of those through December 2005. Of those 55 written requests, 52 (95 percent) resulted in FDA granting pediatric exclusivity. In addition, of the 41 on-patent drugs that drug sponsors declined to study, FDA referred 9 to FNIH, which had not funded the study of any, as of December 2005.

Few of the off-patent drugs identified by NIH as in need of study for pediatric use have been studied. By 2005, NIH had identified 40 off-patent drugs it recommended be studied for pediatric use. Through 2005, FDA issued written requests for 16 of these drugs, and all but one of these written requests were declined by drug sponsors. NIH funded pediatric

[9]GAO, *Pediatric Drug Research: Studies Conducted under Best Pharmaceuticals for Children Act*, GAO-07-557 (Washington, D.C.: Mar. 22, 2007).

drugs studies for 7 of the remaining 15 written requests declined by drug sponsors through December 2005.

Almost all the drugs that have been granted pediatric exclusivity under BPCA—about 87 percent—have had important labeling changes as a result of pediatric drug studies conducted under BPCA, but the process for reviewing the study results and making these changes can be lengthy. 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. The review process took from 238 to 1,055 days when FDA required additional information to support changes in the drug labeling.

Background

BPCA was enacted on January 4, 2002, to encourage drug sponsors to conduct pediatric drug studies.[10] BPCA allows FDA to grant drug sponsors pediatric exclusivity—6 months of additional market exclusivity—in exchange for conducting and reporting on pediatric drug studies. BPCA also provides mechanisms for pediatric drug studies that drug sponsors decline to conduct.

BPCA Process

The process for initiating pediatric drug studies under BPCA formally begins when FDA issues a written request to a drug sponsor to conduct pediatric drug studies for a particular drug. When a drug sponsor accepts the written request and completes the pediatric drug studies, it submits to FDA reports describing the studies and the study results. BPCA specifies

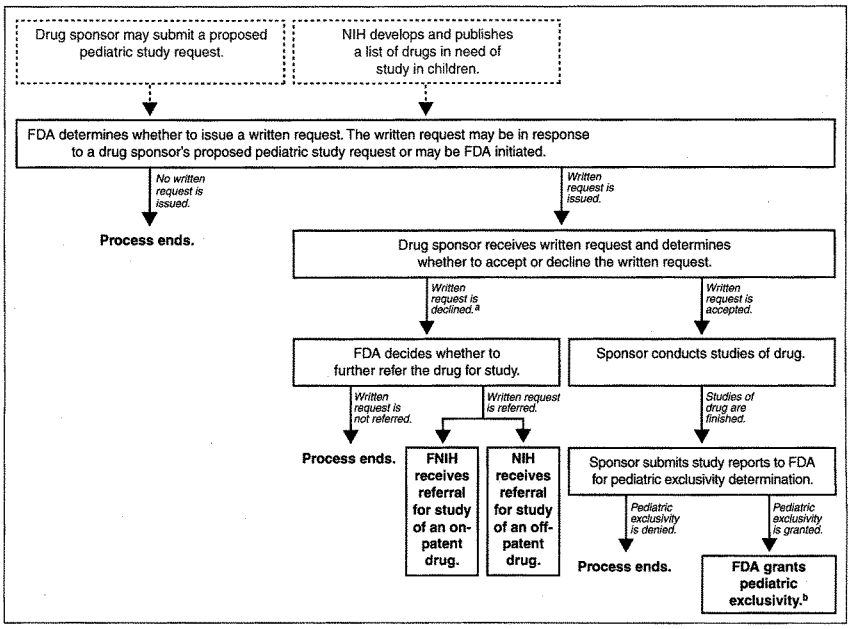
[10]BPCA reauthorized and enhanced the pediatric exclusivity provisions of the Food and Drug Administration Modernization Act of 1997 (FDAMA), Pub. L. No. 105-115, 111 Stat. 2296, which first established incentives for conducting pediatric drug studies—in the form of additional market exclusivity—and whose pediatric exclusivity provisions expired on January 1, 2002. We previously described how FDAMA was responsible for an increase in pediatric drug studies. GAO, *Pediatric Drug Research: Substantial Increase in Studies of Drug for Children, But Some Challenges Remain*, GAO-01-705T (Washington, D.C.: May 8, 2001).

that FDA generally has 90 days to review the study reports to determine whether the pediatric drug studies met the conditions outlined in the written request.[11] If FDA determines that the pediatric drug studies conducted by the drug sponsor were responsive to the written request, it will grant a drug pediatric exclusivity regardless of the study findings.[12] Figure 1 illustrates the process under BPCA.

[11]Under certain circumstances, FDA could have only 60 days to review the study report to determine pediatric exclusivity. However, FDA officials told us that under BPCA, this has never happened. Otherwise, FDA has 90 days to determine if the studies fairly respond to the written request, were conducted in accordance with commonly accepted scientific principles and protocols, and were properly submitted.

[12]Pediatric exclusivity applies to all approved uses of the drug, not just those studied in children. Therefore, if the studies find that the drug is not safe for use by children, the drug will still receive pediatric exclusivity and therefore extended market exclusivity for the adult uses of the drug.

Figure 1: BPCA Process



Source: GAO.

[a]If a drug sponsor of an off-patent drug does not respond to FDA's written request within 30 days, the written request is considered declined. Pediatric exclusivity is not granted to drugs where the drug sponsor declined the written request.

[b]FDA has granted pediatric exclusivity in response to written requests for on-patent drugs only. Under certain circumstances FDA could grant pediatric exclusivity in response to a written request for an off-patent drug.

BPCA Provisions for Pediatric Drug Studies Declined by Drug Sponsors

BPCA includes two provisions to further the study of drugs when drug sponsors decline written requests. FDA cannot extend pediatric exclusivity in response to written requests for any drugs for which the drug sponsors declined to conduct the requested pediatric drug studies.

First, when drug sponsors decline written requests for studies of on-patent drugs, BPCA provides for FDA to refer the study of those drugs to FNIH for funding. FNIH, which is a nonprofit corporation and independent of NIH, supports the mission of NIH and advances research by linking private sector donors and partners to NIH programs. FNIH and NIH collaborate to fund certain projects. As of December 2005, FNIH had raised $4.13 million to fund pediatric drug studies under BPCA.

Second, to further the study of off-patent drugs, NIH—in consultation with FDA and experts in pediatric research—develops a list of drugs, including off-patent drugs, which the agency believes need to be studied in children. NIH lists these drugs annually in the *Federal Register*. FDA may issue written requests for those drugs on the list that it determines to be most in need of study. If the drug sponsor declines or fails to respond to the written request, NIH can contract for, and fund, the pediatric drug studies. Drug sponsors generally decline written requests for off-patent drugs because the financial incentives are considerably limited.

Making Labeling Changes under BPCA for On-Patent Drugs

Pediatric drug studies often reveal new information about the safety or effectiveness of a drug, which could indicate the need for a change to its labeling. Generally, the labeling includes important information for health care providers, including proper uses of the drug, proper dosing, and possible adverse events that could result from taking the drug. FDA may determine that the drug is not approved for use by children, which would then be reflected in any labeling changes.

The agency refers to its review to determine the need for labeling changes as its scientific review. BPCA specifies that study results submitted as a supplemental new drug application—which, according to FDA officials, most are—are subject to FDA's general performance goals for a scientific

review, which in this case is 180 days.[13] FDA's process for reviewing study results submitted under BPCA for consideration of labeling changes is not unique to BPCA. FDA's action can include approving the application, determining that the application is approvable, or determining that the application is not approvable. A determination that an application is approvable may require that drug sponsors conduct additional analyses. Each time FDA takes action on the application, a review cycle is ended.

Drug Sponsors Agreed to Study the Majority of On-Patent Drugs with Written Requests under BPCA, but No Studies Were Conducted When Drug Sponsors Declined the Written Requests

Most of the on-patent drugs for which FDA requested pediatric drug studies under BPCA were being studied, but no studies have resulted when the requests were declined by drug sponsors. From January 2002 through December 2005, FDA issued 214 written requests for on-patent drugs to be studied under BPCA, and drug sponsors agreed to conduct pediatric drug studies for 173 (81 percent) of those.[14] The remaining 41 written requests were declined. Of these 41, FDA referred 9 written requests to FNIH for funding and FNIH had not funded any of those studies as of December 2005.

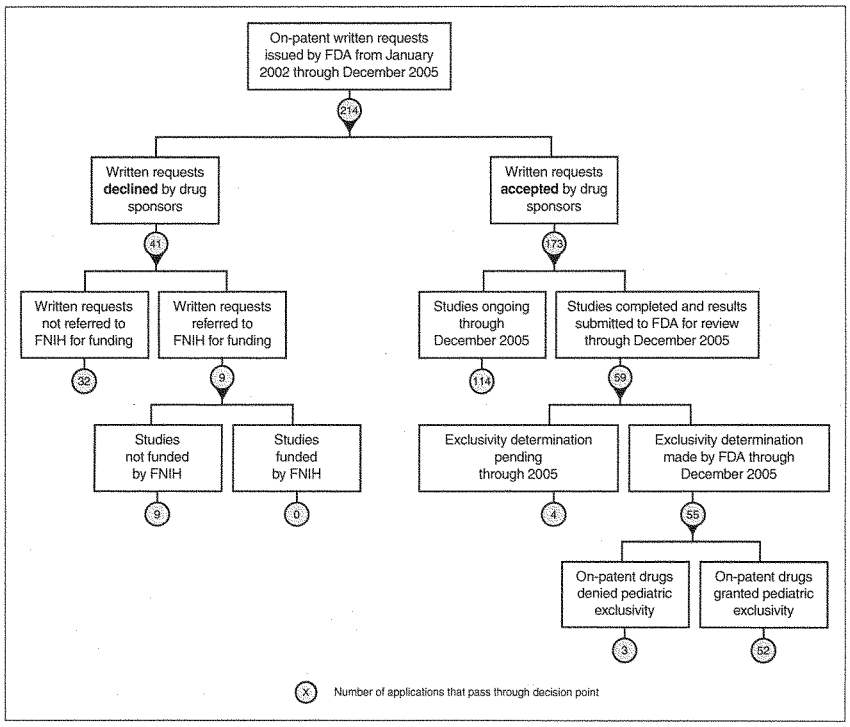
[13]Most drugs studied under BPCA have previously been approved for marketing in the United States, so a supplement to the original "new drug application" is submitted. BPCA requires that supplemental new drug applications submitted by drug sponsors be treated as "priority supplements." FDA's goal is to take action on priority supplements within 180 days. If the drug studied under BPCA was not previously approved for marketing in the United States, the application would be submitted as a new drug application. FDA has a performance goal to review nonpriority new drug applications in 10 months.

[14]Some drugs have two written requests for a variety of reasons. In some cases, FDA may have requested that the drug sponsor study the effects of the drug on different diseases. In other cases, there could be two written requests for the same drug, issued to different drug sponsors for different dosage forms of the drug. In addition, FDA told us that the specified time period for studies to be completed elapsed for some written requests before the completion of studies, and the agency issued new written requests. In all of these situations, we counted each of these written requests separately. Therefore, there are more written requests than there are unique drugs with written requests. Of the 214 written requests issued by FDA, 68 were written requests first issued under BPCA. The remaining 146 written requests were originally issued under FDAMA and reissued under BPCA because drug sponsors had not responded to the written requests or completed the requested pediatric drug studies at the time that BPCA went into effect.

Drug sponsors completed pediatric drug studies for 59 of the 173 accepted written requests—studies for the remaining 114 written requests were ongoing—and FDA made pediatric exclusivity determinations for 55 of those through December 2005.[15] Of those 55 written requests, 52 (95 percent) resulted in FDA granting pediatric exclusivity. Figure 2 shows the status of written requests issued under BPCA for the study of on-patent drugs, from January 2002 through December 2005.

[15]FDA had not completed its review of the study results to determine exclusivity prior to December 2005 for the remaining four drugs.

Figure 2: Status of Written Requests Issued under BPCA for the Study of On-Patent Drugs, from January 2002 through December 2005



Source: GAO.

Note: Written requests issued from January 2002 through December 2005 include new written requests issued under BPCA combined with written requests originally issued under FDAMA but reissued under BPCA.

Drugs were studied under BPCA for their safety and effectiveness in treating children for a wide range of diseases, including some that are common—such as asthma and allergies— and serious or life threatening in children—such as cancer, HIV, and hypertension. We found that the drugs studied under BPCA represented more than 17 broad categories of disease. The category that had the most drugs studied under BPCA was cancer, with 28 drugs. In addition, there were 26 drugs studied for neurological and psychiatric disorders, 19 for endocrine and metabolic disorders, 18 related to cardiovascular disease—including drugs related to hypertension—and 17 related to viral infections. Analyses of two national databases shows that about half of the 10 most frequently prescribed drugs for children were studied under BPCA.

Through December 2005, drug sponsors declined written requests issued under BPCA for 41 on-patent drugs. FDA referred 9 of these 41 written requests (22 percent) to FNIH for funding,[16] but as of December 2005, FNIH had not funded the study of any of these drugs.[17] NIH has estimated that the cost of studying these 9 drugs would exceed $43 million, but FNIH had raised only $4.13 million for pediatric drug studies under BPCA.

Few Off-Patent Drugs Have Been Studied under BPCA

Few off-patent drugs identified by NIH as in need of study for pediatric use have been studied. By 2005, NIH had identified 40 off-patent drugs that it believed should be studied for pediatric use. Through 2005, FDA issued written requests for 16 of these drugs. All but 1 of these written requests were declined by drug sponsors. NIH funded pediatric drug studies for 7 of the remaining 15 written requests declined by drug sponsors through December 2005.

[16]When a drug sponsor of an on-patent drug declines a written request, the agency must determine if there is a continuing need for information relating to the use of the drug in children. Reasons that FDA has concluded that there is not a continuing need include the drug was not yet approved, some part of the study was being performed by the drug sponsor or another party, the drug's patent ended, the risk-benefit assessment shifted, safe alternative therapies were already on the market even though the agency had issued the written request in hope of obtaining additional valuable information, another drug may have been approved or may soon be approved with a better safety record, or there is minimal use of the drug by children.

[17]In April 2006, FNIH agreed to allocate all $4.13 million it had raised for pediatric drug studies under BPCA to fund half of the cost to study one on-patent day—baclofen. NIH expects the cost of the study of baclofen to be about $7.8 million over three years and NIH agreed to cover the costs of the study that exceed the contribution from FNIH. Because FNIH has committed all of its BPCA funds to the study of baclofen, there are no resources left for FNIH to fund the study of any other drugs.

NIH provided several reasons why it has not pursued the study of some off-patent drugs that drug sponsors declined to study. Concerns about the incidence of the disease that the drugs were developed to treat, the feasibility of study design, drug safety, and changes in the drugs' patent status have caused the agency to reconsider the merit of studying some of the drugs it identified as important for study in children.[18] For example, in one case NIH issued a request for proposals to study a drug but received no responses. In other cases, NIH is awaiting consultation with pediatric experts to determine the potential for study.

Further, NIH has not received appropriations specifically for funding pediatric drug studies under BPCA. NIH anticipates spending an estimated $52.5 million for pediatric drug studies associated with 7 written requests issued by FDA from January 2002 through December 2005.[19]

Most Drugs Granted Pediatric Exclusivity under BPCA Had Labeling Changes, but the Process for Making Changes Was Sometimes Lengthy

Most drugs that have been granted pediatric exclusivity under BPCA—about 87 percent—have had labeling changes as a result of the pediatric drug studies conducted under BPCA. Pediatric drug studies conducted under BPCA showed that children may have been exposed to ineffective drugs, ineffective dosing, overdosing, or side effects that were previously unknown. However, the process for reviewing study results and completing labeling changes was sometimes lengthy, particularly when FDA required additional information from drug sponsors to support the changes.

Of the 52 drugs studied and granted pediatric exclusivity under BPCA from January 2002 through December 2005, 45 (about 87 percent) had labeling changes as a result of the pediatric drug studies. In addition, 3 other drugs had labeling changes prior to FDA making a decision on granting pediatric exclusivity. FDA officials said that the pediatric drug studies conducted up to that time provided important safety information that should be reflected in the labeling without waiting until the full study results were submitted or pediatric exclusivity determined.

[18]Since its inception, no drug has been removed from the list published in the *Federal Register*, regardless of the feasibility or likelihood of it being studied.

[19]The costs reported by NIH are estimates, which may change during the course of the studies.

Pediatric drug studies conducted under BPCA have shown that the way that some drugs were being administered to children potentially exposed them to an ineffective therapy, ineffective dosing, overdosing, or previously unknown side effects—including some that affect growth and development. The labeling for these drugs was changed to reflect these study results. For example, studies of the drug Sumatriptan, which is used to treat migraines, showed that there was no benefit derived from this drug when it was used in children. There were also certain serious adverse events associated with its use in children, such as vision loss and stroke, so the labeling was changed to reflect that the drug is not recommended for children under 18 years old.

Other drugs have had labeling changes indicating that the drugs may be used safely and effectively by children in certain dosages or forms. Typically, this resulted in the drug labeling being changed to indicate that the drug was approved for use by children younger than those for whom it had previously been approved. In other cases, the changes reflected a new formulation of a drug, such as a syrup that was developed for pediatric use, or new directions for preparing the drug for pediatric use were identified in the pediatric drug studies conducted under BPCA.

Although FDA generally completed its first scientific review of study results—including consideration of labeling changes—within its 180-day goal, the process for completing the review, including obtaining sufficient information to support and approve labeling changes, sometimes took longer. For the 45 drugs granted pediatric exclusivity that had labeling changes, it took an average of almost 9 months after study results were first submitted to FDA for the sponsor to submit and the agency to review all of the information it required and approve labeling changes. For 13 drugs (about 29 percent), FDA completed this scientific review process and approved labeling changes within 180 days. It took from 181 to 187 days for the scientific review process to be completed and labeling changes to be approved for 14 drugs (about 31 percent). For the remaining 18 drugs (about 40 percent), FDA took from 238 to 1,055 days to complete the scientific review process and approve labeling changes. For 7 of those drugs, it took more than a year to complete the scientific review process and approve labeling changes.

While the first scientific reviews were generally completed within 180 days, it took 238 days or more for 18 drugs.[20] For those 18 drugs, FDA determined that it needed additional information from the drug sponsors in order to be able to approve the drugs for pediatric use. This often required that the drug sponsor conduct additional analyses or pediatric drug studies. FDA officials said they could not approve any changes to drug labeling until the drug sponsor provided this information. Drug sponsors sometimes took as long as 1 year to gather the additional necessary data and respond to FDA's request.[21]

Mr. Chairman, this concludes my prepared remarks. I would be pleased to respond to any questions that you or other members of the Subcommittee may have.

For further information regarding this testimony, please contact Marcia Crosse at (202) 512-7119 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this testimony. Thomas Conahan, Assistant Director; Carolyn Feis Korman; and Cathleen Hamann made key contributions to this statement.

[20]FDA considers itself in conformance with its review goals even though the entire process often took longer than 180 days.

[21]BPCA provides a dispute resolution process that FDA can use to resolve disagreements with drug sponsors regarding labeling of on-patent drugs where the only remaining issue concerns the labeling. FDA officials said they have never used this process because labeling has never been the only unresolved issue for those drugs for which the review period exceeded 180 days. Agency officials told us that reminding the drug sponsors that such a process exists has motivated drug sponsors to complete labeling change negotiations by reaching agreement with FDA.

Mr. PALLONE. Thank you, Dr. Crosse. Dr. Gorman.

STATEMENT OF RICHARD L. GORMAN, M.D., F.A.A.P., CHAIR, AAP SECTION OF CLINICAL PHARMACOLOGY AND THERAPEUTICS, AMERICAN ACADEMY OF PEDIATRICS

Dr. GORMAN. Mr. Chairman and members of the committee, I am Richard Gorman, a pediatrician and member of the American Academy of Pediatrics, and I have practiced pediatrics for over 25 years taking care of infants, children, and adolescents in my private practice. I thank the committee for having this hearing on the need for safe and effective medicines.

It is through my practice, Pediatric Partners in Ellicott City that I see firsthand the therapeutic benefits of increased information on drugs used in children. With over 80,000 pediatric visits annually in our four clinical sites in three counties in Maryland, my partners and I can attest to the importance of pediatric drug studies and the legislation that supports them.

I am here today on behalf of the American Academy of Pediatrics to discuss the BPCA and the Pediatric Research Equity Act which represent critical public policy successes for children.

I begin my testimony today by saying without reservation that in the last decade we have gained more useful information on drugs through BPCA and PREA than we have had in the previous 70 years. 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 these drugs where previously there was none. Since the passage of FDAMA over a decade ago, FDA has requested nearly 800 studies involving more than 45,000 children in pediatric trials. The information gained from these studies have resulted in label changes for 128 drugs. Medical and clinical pharmacology review summaries of over 76 drugs are now publicly available on the FDA's Web site. It is vitally important that these laws be reauthorized.

In previous testimony before Congress, I have described children as the canaries in the mine shaft, acting as early warnings of unknown dangers in therapeutics. BPCA and PREA working together have changed this by creating an effective, two-pronged approach to generating new pediatric studies. PREA provides FDA the authority to require pediatric studies of drugs when their uses for children would be the same as adults. BPCA provides voluntary incentives to drug manufacturers for an additional 6 months of marketing exclusivity for conducting pediatric studies of drugs that FDA determines may be useful for children.

Despite these important advances, there is much more we still need to do. Children remain second-class citizens when it comes to drug safety and efficacy information. Currently two-thirds of the drugs used in children are not labeled for them. Almost 80 percent of hospitalized children receive at least one drug prescribed for them for an off-label use. For children, off-label use remains the rule and not the exception. Both BPCA and PREA are crucially important and must be reauthorized this year, including needed improvements.

The FDA bill recently passed in the Senate reauthorizes BCPA and PREA, and we applaud the Senate's work. The studies gen-

erated under BPCA provide information beyond safety and produce information on dosing, efficacy, and importantly the lack of efficacy and off-label use.

PREA created a new presumption that all drugs would, in fact, be studied in children at the time of the application, thus preventing the need for a safety program to trigger drug studies after the drug is on the market. Mr. Chairman, in my written testimony I have elaborated on recommendations for improvement to BPCA and PREA in several areas. The American Academy of Pediatrics urges this committee to pass a reauthorized bill which increases the dissemination, the transparency, and the tracking of pediatric drug information; streamlines and integrates the Food and Drug Administration's administration of BPCA and PREA to improve the uniformity, consistency, and quality of pediatric studies; expands the study of off-patent drugs and generic drugs and addresses the gaps in understandings of pediatric therapeutics; and crafts a balanced compromise that will preserve both the quality and the number of pediatric studies gained through BPCA's exclusivity extension and also addresses the concerns regarding excessive revenues for blockbuster drugs. And lastly, the AAP wants PREA to become a permanent part of the Food and Drug Act and allow for the periodic re-evaluation of BPCA to ensure that incentives remain fair and continue to yield pediatric information.

In 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 Best Pharmaceuticals for Children and the Pediatric Research Equity Act. We urge their improvement and renewal for the sake of all children throughout the United States. I will be glad to answer any questions you may have.

[The prepared statement of Dr. Gorman follows:]

American Academy of Pediatrics

TESTIMONY OF
RICHARD L. GORMAN, MD, FAAP
on behalf of the
AMERICAN ACADEMY OF PEDIATRICS

before the

COMMITTEE ON ENERGY AND COMMERCE
SUBCOMMITTEE ON HEALTH

UNITED STATES HOUSE OF REPRESENTATIVES

MAY 22, 2007

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Richard L. Gorman, MD, FAAP
Testimony before the Committee on Energy and Commerce, Subcommittee on Health
May 22, 2007

Chairman Pallone, members of the committee, I am Richard Gorman, MD, FAAP, a practicing pediatrician who has taken care of infants, children and adolescents for over 25 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 first-hand 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. I would also like to express the Academy's strong support for new legislation to improve access and safety of medical devices used in children.

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 seventy years.

The Senate has recently voted by 93-1 to reauthorize BPCA and PREA. AAP applauds the Senate's action. 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 six 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 128 drugs.[1] By comparison, in the seven years prior to FDAMA, only 11 studies of marketed drugs were completed, though 70 studies were promised. While similar data tracking PREA's effectiveness is not been publicly available, FDA's website credits 55 label changes to PREA. AAP hopes this year's reauthorization will improve tracking and reporting of PREA's results.

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 what 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®);
- 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®, Paxil®, et al.);
- 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."

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

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 and has 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% 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.

New drug safety legislation has been passed in the Senate and similar legislation has been introduced in the House. Such legislation is a needed complement to the tools provided by BPCA and PREA and will enhance, not duplicate, the available information families and providers have about drugs used in children. The studies generated under BPCA provide information far beyond safety and produce information on dosing, efficacy – and importantly – lack of efficacy in off-label use. PREA created a new presumption that all new drugs would be studied in children at the time of application thus preventing the need for a safety problem to trigger studies after the drug is on the market.

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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

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, should not then the drug label reflect that study? The Government Accountability Office (GAO) found that about 87% 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.

The transparency of BPCA's written request process 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 website. 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 oversight 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

[4] GAO 2007; 16

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. AAP 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 FNIH 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 the 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. AAP 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 drug sponsors agreed to conduct studies in response to a written request from FDA 81% 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

[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.
[7] GAO 2007; 12

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. The exclusivity adjustment crafted by Senator Dodd in S. 1082 meets AAP criteria and we urge the Committee to adopt this approach.

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 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.

SUPPORT FOR H.R. 1494, THE PEDIATRIC MEDICAL DEVICE SAFETY AND IMPROVEMENT ACT

I also express AAP's strong support of H.R. 1494 and our sincere gratitude to Representatives Markey and Rogers for championing this important legislation necessary for achieving safe and effective medical devices for all children. We also thank Representatives Capps, Eshoo, Grijalva and Ramstad for cosponsoring the bill.

The Pediatric Medical Device Safety and Improvement Act of 2007, H.R. 1494, 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. This bill strikes the right balance between new incentives and increased postmarket surveillance and puts forward a comprehensive package that serves a critical step forward 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 improving pediatric medical device development.

Facilitating pediatric device development and manufacture through mentorship. The bill also establishes six-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 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 a 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. H.R. 1494 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. The Institute of Medicine (IOM) studied post-market safety for pediatric medical devices for more than a year and 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. The 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.[8]

[8] 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.

> 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.[9]

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 frequently 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. New post-market authority can address the current limited amount of available data on devices for children and create a mechanism for ensuring that needed pediatric studies are conducted for a sufficient length of time.

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 as well as H.R. 1494. We urge swift passage by this committee for the sake of all children throughout the United States.

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

Richard L. Gorman, MD, FAAP

[9] IOM, p. 226.

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Pediatric studies lead to more information on drug labels

Children, parents and medical practitioners are now benefiting from information on the many new pediatric drug labels approved by the Food and Drug Administration (FDA) as part of a national initiative to ensure that there is scientific information on the safe and effective use of drugs in children.

Useful new pediatric information is now part of product labeling for 119 drugs (as of September 2006). This information was generated by more than 300 studies in pediatric patients conducted under the pediatric exclusivity incentive program established by the Food and Drug Administration Modernization Act of 1997 (FDAMA) and reauthorized by the Best Pharmaceuticals for Children Act of 2002 (BPCA).

The cumulative list of all labeling change summaries resulting from FDAMA and BPCA can be found at www.fda.gov/cder/pediatric/labelchange. htm. *AAP News* published previous listings of labeling changes in April 2001 and August 2003.

This article describes *select* subsequent pediatric labeling changes made due to the incentive program. The labeling changes for the drugs described here represent changes that affect a large number of children because they mitigate serious and life-threatening diseases and/or treat very common childhood diseases or provide vital new information on the use of the product in children. In addition, drug approvals that affect vulnerable populations such as neonates or children with other chronic and/or underlying health issues (e.g., neurological impairment, mental illness) also are highlighted.

Common pediatric conditions

Obesity, headaches, depression and behavioral issues related to attention-deficit/hyperactivity disorder and seizures are common reasons for pediatric office visits. Labeling changes for orlistat, sumatriptan, methylphenidate, mixed amphetamine salts and levetiracetam will assist the practitioner in choosing therapies and counseling patients regarding the safe use of these products.

Xenical (orlistat) for obesity management is supported in adolescent patients ages 12 to 16 years based on studies in adults with additional safety and efficacy data from a year-long trial in obese adolescent patients. Since treatment with orlistat can reduce the absorption of fat-soluble vitamins, all patients should take a daily multivitamin supplement.

In contrast, data from pediatric studies of **Meridia (sibutramine)** were inadequate to recommend use of sibutramine for the treatment of obesity in pediatric patients. The risk of suicidal behavior or thinking in pediatric patients treated with sibutramine is unknown.

Imitrex (sumatriptan) Nasal Spray studies for the treatment of migraines in adolescents ages 12 to17 years did not show drug effectiveness compared to placebo. The use of sumatriptan in patients younger than 18 years is not recommended. Serious adverse events have occurred, similar in nature to those reported rarely in adults, including stroke, visual loss and death. Imitrex is approved for the treatment of migraines in adults.

Effexor (venlafaxine), Remeron (mirtazapine), Paxil (paroxetine), Serzone (nefazodone), Zoloft (sertraline) and Celexa (citalopram) are among the antidepressants recently studied in pediatric patients for which efficacy was not demonstrated when used to treat depression. Boxed warnings regarding suicidality were incorporated into labeling for antidepressants in this class based on results from BPCA studies. Of these, only sertraline is approved for use in pediatric patients. Sertraline is indicated for the treatment of obsessive-compulsive disorder in children 6 to 17 years. Monitor patients for clinical worsening, suicidality and unusual changes in behavior; growth also should be monitored in children receiving sertraline.

Concerta (methylphenidate hydrochloride) is approved to treat attention-deficit/hyperactivity disorder (ADHD) in children 6 to 17 years of age. Studies in adolescents 13 to 17 years old resulted in a higher maximum recommended dosage for adolescents compared to 6- to 12-years-olds for patients new to methylphenidate because of an increased apparent oral clearance in the older adolescent. In contrast, the maximum recommended dosage of **Adderall XR (mixed amphetamine salts)** for adolescents is lower than that for children 6 to 12 year olds.

Keppra (levetiracetam) approval for adjunctive therapy in the treatment of partial onset seizures in children was extended down to age 4 years. Behavioral symptoms and somnolence were observed in a higher percentage of pediatric patients treated compared with adults. Similarly, the age range for **Trileptal (oxcarbamazepine)** was extended down to 2 years of age for the adjunctive treatment of partial seizures.

HIV

Even though therapies for HIV are being studied in children, obtaining information on the effects of therapy in the youngest children and neonates has remained problematic. Developmental changes in infants, such as changes in the metabolism of drugs related to maturation of kidney function or liver enzyme systems, affect pharmacodynamics and potentially drug dosing. Thus, con-

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ducting studies to determine appropriate dosing in neonates and young children is essential.

HIV-infected infants younger than 12 months are considered at high risk for disease progression. Combination therapy is recommended for all infants, children and adolescents who are treated with antiretroviral agents. When compared with monotherapy, combination therapy slows disease progression and improves survival, results in a greater and more sustained virologic response, and delays development of viral resistance to the antiretroviral agents being used.

Treatment with the protease inhibitor class of antiretrovirals became common practice in the treatment of HIV-infected pediatric patients in the late-1990s. Since then, there have been several FDA-approved formulations appropriate for infants and children who cannot swallow pills. Both nelfinavir and ritonavir, listed below, have approved formulations appropriate for young children.

Viracept (nelfinavir) is a protease inhibitor that can be used in combination therapy for the treatment of HIV infection. Nelfinavir was the most frequently used protease inhibitor from 1998-2002, and in 2003, was the second most frequently used (27.3%). The studies performed under BPCA provided information on twice-daily dosing and three-times daily dosing in pediatric patients, and demonstrated that under the age of 2 years, it is difficult to establish a reliable effective dose.

Norvir (ritonavir) is another protease inhibitor used in combination with other drugs to treat HIV-infected pediatric patients. Pediatric studies extended the age range down to 1 month. Ritonavir is mainly used now to increase the serum concentrations and decrease the dosage frequency of other protease inhibitors.

Cancer

Studying products to treat cancer in children is challenging because of the limited numbers of cases and numerous types of pediatric cancers that manifest themselves differently in children than in adults. For example, while clofarabine is effective in the treatment of pediatric cancer, irinotecan has not proven to be effective. Ondansetron is useful for treating or preventing chemotherapy-induced nausea and vomiting.

Clolar (clofarabine) is approved for the treatment of pediatric patients 1 to 21 years of age with relapsed or refractory acute lymphoblastic leukemia. A single arm study conducted in pediatric patients, who had relapsed after and/or were refractory to two or more prior therapies, provided information on proper dosing, PK parameters and the adverse event profile of the drug. The product was shown to increase survival or provide other clinical benefits.

Camptosar (irinotecan) studies demonstrated that the product should not be used in children with rhabdosarcoma based on a greater mortality and a more rapid progression of disease when on drug.

Zofran (ondansetron) Injection studies established dosing for the prevention of chemotherapy-induced nausea and vomiting for children 6 to 48 months old. The pharmacokinetic trials revealed that children less than 18 years of age cleared the product faster than adults. On the other hand, in children 1 to 4 months of age, clearance was slower than in patients who were 4 to 24 months of age. Pediatric studies also established dosing for the prevention of post-operatively induced nausea and vomiting for children 1 to 24 months old.

Infectious diseases

Infectious diseases are one of the most frequent reasons for pediatric office visits or hospitalization. Antiviral therapies such as oseltamivir and antibacterials such as ciprofloxacin, ertapenem and linezolid are important additions to the pediatric armamentarium.

Tamiflu (oseltamivir) is indicated for the prophylaxis and treatment of uncomplicated acute influenza and was studied in pediatric patients down to 1 year of age. Oseltamivir is not recommended for children younger than 1 year of age due to safety concerns. Additional post-marketing information also has raised the issue of unusual and sometimes injurious behavior in some children after receiving this product.

Cipro (ciprofloxacin), while indicated for complicated urinary tract infection and pyelonephritis, is not a drug of first choice due to increased adverse events compared to controls, including events related to joints and/or surrounding tissues.

Invanz (ertapenem) is indicated for the treatment of serious infections, including complicated intra-abdominal infections, complicated skin infections, community acquired pneumonia, complicated urinary tract infections and acute pelvic infections. However, pediatric studies demonstrated that this antibiotic should not be used in meningitis because the drug did not sufficiently penetrate the central nervous system.

Zyvox (linezolid) is used to treat infections caused by bacteria that are resistant to other antibiotics (e.g., *Staphylococcus aureus* (MRSA), other methicillin-resistant staphylococcus species (MRSS) and penicillin-resistant *Streptococcus pneumoniae* (PRSP)). These infections occur in children with ventriculoperitoneal shunts but unfortunately in these patients, drug levels were not high enough in the brain to treat central nervous system infection. Thus, linezolid is not recommended for the treatment of pediatric patients with central nervous system infections.

Vulnerable subpopulations

In the past, investigators have been reluctant to perform studies in vulnerable subpopulations such as neonates and children with neurological disorders, chronic pain, anorexia nervosa and orphan conditions. As a result of BPCA, trials are being conducted in children with these conditions, and important information regarding therapies for these conditions has been generated.

Dosing guidelines for maintenance of anesthesia in patients from birth to 2 months for **Ultiva (remifentanil)** have been incorporated into labeling. Safety and efficacy have been established from birth to 1 year and older.

Detrol LA (tolterodine) is indicated for the treatment of adults with overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. However, a study in children ages 5 to 10 years revealed an increased number of urinary tract infections, aggressive, abnormal and hyperactive behavior, and attention disorders in patients treated with this drug when compared to placebo. In addition, the studies did not demonstrate efficacy. Therefore, tolterodine is not approved for use in children.

Duragesic (fentanyl) is indicated in the management of chronic pain in opioid-tolerant children 2 years and older who require continuous opioid analgesia for pain. Studies provided information for dosing in pediatric patients, and the one year post-exclusivity safety review demonstrated serious safety concerns when this drug was

inappropriately used for acute pain (such as post-surgical pain) in opioid naïve patients.

Ortho Tri-Cyclen (norgestimate/ethinyl estradiol) use in adolescent females with anorexia nervosa to improve bone mineral density is not recommended since in clinical trials no significant difference in bone mineral density was observed. The drug is approved for birth control and the treatment of acne in patients 15 years and older.

Fosamax (alendronate) use in children with severe osteogenesis imperfecta is not recommended based on studies in children ages 4 to 18 years old. In these trials, treatment with alendronate did not reduce the risk of fracture.

The cumulative list of all labeling change summaries resulting from FDAMA and BPCA can be found at www.fda.gov/cder/pediatric/labelchange.htm. An excerpt from this list containing details of the labeling changes that are highlighted here as well as labeling summaries approved from January 2005 to September 2006 appears below:

Pediatric Exclusivity Labeling Changes from August 1, 2003 through September 29, 2006

Exclusivity Granted/ (Labeled)	Product	Labeled Indications Resulting from Pediatric Studies	Labeling Changes
9/12/03 (12/12/03)	Orlistat Xenical (Roche)	Obesity management	• Use in 12-16 year olds is supported by studies in adults with additional data from a 54 week safety and efficacy study in obese adolescent patients. • Since orlistat can reduce absorption of fat soluble vitamins, all patients should take a daily multivitamin supplement containing fat soluble vitamins. • Adverse event profile in adolescent patients was similar to that seen in adults
3/15/00 (3/8/04)	Remifentanil Ultiva (Abbott)	Maintenance of anesthesia	• Safety and efficacy for the maintenance of anesthesia established from birth to 1 year of age • Recommended dosing guidelines for maintenance of anesthesia for patients from birth to 2 months • The clearance rate observed in neonates was highly variable – approximately 2 times higher than young healthy adults • Individual doses for each patient should be carefully titrated
9/4/03 (3/19/04)	Nelfinavir Viracept (Pfizer)	Treatment of HIV-1	• Safety and effectiveness established in patients 2–13 years of age • New twice daily dosing regimen and modified three times daily dosing for pediatric patients ≥2 years • A reliably effective dose not established in patients <2 years of age • PK information in pediatric patients from birth to 13 years of age • Highly variable drug exposure is a significant problem in pediatric patients • Adverse event profile was similar to that for adults
12/18/03 (3/25/04)	Ciprofloxacin Cipro (Bayer)	Complicated UTI and pyelonephritis	• Indicated for the treatment of complicated urinary tract infections (cUTIs) and pyelonephritis in pediatric patients 1–17 years of age • Not drug of first choice due to increased adverse events compared to controls including events related to joints and/or surrounding tissues • Information on PK and dose in pediatric patients 1–17 years of age • The most frequent adverse events observed within 6 weeks of treatment initiation during the cUTI clinical trial were gastrointestinal 15% compared to 9% and musculoskeletal 9.3% compared to 6% in ciprofloxacin-treated compared to control-treated patients, respectively

Exclusivity Granted/ (Labeled)	Product	Labeled Indications Resulting from Pediatric Studies	Labeling Changes
1/5/04 (4/14/04)	Tolterodine Detrol LA (Pfizer)		• Efficacy in pediatric population has not been demonstrated • The dose-plasma concentration relationship is linear in patients from 11 to 15 years • Parent/metabolite ratios differed according to CYP2D6 metabolizer status • 710 pediatric patients ages 5-10 years with urinary frequency and urge incontinence were studied in 2 randomized placebo controlled trials. Urinary tract infections were higher in patients treated with Detrol LA (6.6%) compared to placebo (4.5%) • Aggressive, abnormal and hyperactive behavior and attention disorders occurred in 2.9% of children treated with Detrol LA compared to 0.9% treated with placebo
Boxed Warning for Antidepressants			FDA required boxed warning for all antidepressants: Suicidality in (1/26/05) Children and Adolescents — Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [insert established name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Insert established name] is not approved for use in pediatric patients **or** is approved for pediatric patients with [Insert approved pediatric indication(s)]. (See Warnings and Precautions: Pediatric Use) Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive-compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.
12/2/02 (5/5/04) [2/18/05]*	Venlafaxine Effexor and Effexor XR (Wyeth)		• Effectiveness in pediatric patients has not been established • See Antidepressant Boxed Warning • 18% of Effexor XR treated patients (6-17 years) versus 3.6% of placebo treated patients experienced a weight loss of at least 3.5% in both MDD and the GAD studies • In an open-label study increases in weight were less than expected based on data from age and sex matched peers. The difference between observed weight gain was larger for children less than 12 years than for adolescents older than 12 years • During an 8 week placebo controlled GAD trial, Effexor XR treated patients ages 6-17 years grew an average of 0.3 cm, while placebo treated patients grew an average of 1 cm. In a 6 month open-label study, height increases that were less than expected based on data from age and sex matched pairs. The difference between observed and expected growth rates were larger for children less than 12 years than for adolescents older than 12 years • Decreased appetite observed in 10% of patients ages 6-17 years old receiving Effexor XR • Occurrence of blood pressure and cholesterol increases considered clinically relevant in pediatric patients similar to that observed in adults

Exclusivity Granted/ (Labeled)	Product	Labeled Indications Resulting from Pediatric Studies	Labeling Changes
3/10/04 (6/24/04)	Irinotecan Camptosar (Pfizer)		• Effectiveness in pediatric patients has not been established • Adverse event profile from a Phase 2 trial with 170 children with refractory solid tumors comparable to that seen in adults; Grade 3-4 neutropenia experienced by 54 (31.8%) patients, neutropenia complicated by fever in 15 (8.8%) patients, Grade 3-4 diarrhea observed in 35 (20.6%) patients. • Accrual for phase 2 study with 21 children with previously untreated rhabdomyosarcoma halted due to high rate (23.6%) of progressive disease and early deaths (14%) • Adverse event profile seen in the 21 children different than that observed in adults; most significant Grade 3 or 4 adverse events were dehydration experienced by 6 patients (28.6%) associated with severe hypokalemia in 5 patients (23.8%) and hyponatremia in 3 patients (14.3%); in addition Grade 3-4 infection was reported in 5 patients (23.8%) (across all courses of therapy and irrespective of causal relationship) • PK parameters comparable to adults • Minimal accumulation of irinotecan and SN-38 (active metabolite) observed in children on daily dosing
3/22/04 (6/24/04)	Oseltamivir Tamiflu (Roche)	Treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older	• Not recommended in pediatric patients less than 1 year of age because of uncertaintiesregarding the rate of development of the human blood-brain barrier and the unknown clinical significance of animal toxicology data for human infants
2/18/04 (10/13/04)	Sumatriptan Imitrex Nasal Spray (Glaxo)		• Five clinical trials evaluating oral sumatriptan in pediatric patients ages 12-17 years didnot establish the safety and effectiveness when compared to placebo • Postmarketing experience documents that serious adverse events (AEs) rarely reported in adults, including stroke, visual loss, and death have occurred in the pediatric population after use of subcutaneous, oral, and/or nasal sumatriptan. • Since clinical data to determine the frequency of serious adverse events in pediatric patients who might receive injectable, oral, and/or intranasal sumatriptan are not presently available, the use of sumatriptan in patients aged younger than 18 years is not recommended.
12/4/03 (10/21/04)	Methylphenidate Concerta (Alza)	ADHD	• Expanded labeling for 13-17 year olds including information on dose, PK parameters, and AE profile • Increase in age resulted in increased apparent oral clearance • For patients new to methylphenidate: higher maximum recommended dosage for adolescents compared to children 6-12 years of age • Data are inadequate to determine whether chronic use of stimulants in children may cause suppression of growth. Therefore, growth should be monitored during treatment • Safety and efficacy in children <6 years have not been established
7/14/04 (12/28/04)	Clofarabine Clolar (Genzyme)	Treatment of relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens	• Labeling for patients 1 to 21 years old. This use is based on the induction of complete responses • Randomized trials demonstrating increased survival or other clinical benefit have not been conducted • Information on dose, PK parameters, and AE profile
(1/12/05)	Mirtazapine Remeron (Organon)		• Safety and effectiveness in the pediatric population have not been established • See Antidepressant Boxed Warning • Two placebo-controlled trials in 258 pediatric patients with MDD have been conducted with Remeron and the data were not sufficient to support a claim for use in pediatric patients

Exclusivity Granted/ (Labeled)	Product	Labeled Indications Resulting from Pediatric Studies	Labeling Changes
6/27/02 (1/12/05)	Paroxetine Paxil (Glaxo)		• Safety and effectiveness in the pediatric population have not been established • See Antidepressant Boxed warning • Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with Paxil, and the data were not sufficient to support a claim for use in pediatric patients
6/27/02 (1/12/05)	Nefazodone Serzone (BMS)		• Safety and effectiveness in the pediatric population have not been established • See Antidepressant Boxed Warning • Two placebo-controlled trials in 286 pediatric patients with MDD have been conducted with Serzone, and the data were not sufficient to support a claim for use in pediatric patients
2/1/02 (2/18/05)	Sertraline Zoloft (Pfizer)		• Safety and effectiveness in the pediatric population other than pediatric patients withOCD have not been established • See Antidepressant Boxed Warning • Two placebo controlled trials in 373 pediatric patients with MDD have been conducted with Zoloft, and the data were not sufficient to support a claim for use in pediatric patients
7/12/02 (2/18/05)	Citalopram Celexa (Forest)		• Safety and effectiveness in the pediatric population have not been established • See Antidepressant Boxed Warning • Two placebo-controlled trials in 407 pediatric patients with MDD have been conducted with Celexa, and the data were not sufficient to support a claim for use in pediatric patients
11/17/04 (3/11/05)	Sirolimus Rapamune (Wyeth)	Prophylaxis of organ rejection in patients undergoing renal transplants	• Safety and efficacy established in children 13 years or older judged to be at low to moderate immunologic risk • Safety was assessed in a controlled clinical trial in pediatric (<18 years of age) renal transplant recipients considered high immunologic risk. The use of Rapamune in combination with calcineurin inhibitors and corticosteroids was associated with an increased risk of deterioration of renal function, lipid abnormalities, and urinary tract infections • Safety and efficacy have not been established in pediatric patients less than 13 years old or in pediatric renal transplant recipients considered at high immunologic risk • Information on PK parameters, adverse events and safety
12/1/04 (3/25/05)	Ondansetron Zofran (Glaxo)	Prevention of chemotherapy-induced and postoperative induced nausea and vomiting	• Established dosing for surgical patients down to 1 month from 2 years of age • Established dosing for cancer patients down to 6 months from 4 years of age • Surgical and cancer patients <18 years tend to have a higher ondansetron clearance compared to adults leading to a shorter half-life in most pediatric patients • The clearance of ondansetron in patients 1-4 months of age is slower and the half-life is approximately 2.5 fold longer than patients who are >4 – 24 months of age • Patients <4 months of age receiving this drug should be closely monitored • Additional information on dose, PK parameters, AE profile and safety
1/27/05 (4/26/05)	Gemcitabine Gemzar (Lilly)		• Effectiveness in pediatric patients has not been demonstrated • Phase 1 trial in pediatric patients with refractory leukemia demonstrated a maximum tolerated dose; however, no meaningful clinical activity observed in a Phase 2 trial of gemcitabine in 22 patients with relapsed acute lymphoblastic leukemia and 10 patients with acute myelogenous leukemia • Toxicities observed were similar to those reported in adults

Exclusivity Granted/ (Labeled)	Product	Labeled Indications Resulting from Pediatric Studies	Labeling Changes
2/11/05 (12/19/02; 5/12/05)	Linezolid Zyvox (Pfizer)	Nosocomial pneumonia, community-acquired pneumonia, complicated and uncomplicated skin and skin structure infections, and vancomycin-resistant infections caused by susceptible strains (12/19/02)	• Extended age range down to birth for nosocomial pneumonia, community-acquired pneumonia, complicated skin and skin structure infections and vancomycin-resistant infections. Safety and efficacy extrapolated from studies in adults and supported by PK and comparator-controlled studies in patients from birth to 11 years • Extended age range down to 5 years of age for uncomplicated skin and skin structure infections based upon a comparator-controlled study in 5 to 17 year olds • Clearance of linezolid varies as a function of age; As age of pediatric patients increases, clearance gradually decreases, and by adolescence mean clearance values approach those observed in adults • Pediatric patients exhibit wider variability in clearance and systemic exposure (area under the curve) compared with adults • New every 8 hours dosing regimen for pediatric patients birth to 11 years of age and every 12 hours dosing regimen for pediatric patients 12 years and older • Information on PK parameters, AE profile, laboratory changes, dosing, and clinical studies (5/12/05) • PK data in pediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) concentrations; therapeutic concentrations were not consistently achieved or maintained in the CSF • Use of linezolid for the empiric treatment of pediatric patients with central nervous system infections is not recommended • Additional information on efficacy in pediatric patients with infectious vancomycin-resistant *Enterococcus faecium*
12/18/03 (5/13/05)	Norgestimate/ ethinyl estradiol Ortho Tri-Cyclen (Ortho McNeil)		• No significant difference between Ortho Tri-Cyclen and placebo in mean change in total lumbar spine (L1-L4) and total hip bone mineraldensity in 123 adolescent females with anorexia nervosa in a double-blind, placebo-controlled, multicenter, one-year clinical trial
2/11/05 (5/18/05)	Ertapenem Invanz (Merck)	Complicated intra-abdominal infections; complicated skin and skin structure infections; community acquired pneumonia; complicated urinary tract infections; acute pelvic infections	• Approved for use down to 3 months of age. Efficacy extrapolated from studies in adultsand supported by PK and safety studies in pediatric patients • Not recommended in infants under 3 months of age as no data are available • Not recommended in the treatment of meningitis in the pediatric population due to lack of sufficient CSF penetration • Information on dose, PK parameters, AE profile and clinical studies
(6/21/05)	Levetiracetam Keppra (UCB Inc)	Adjunctive therapy in the treatment of partial onset seizures in patients with epilepsy	• Extended indication from adults to patients 4 years and older • Safety and effectiveness have not been established in patients less than 4 years of age • PK analysis showed that clearance increased with an increase in body weight • Approximately 22% increase of apparent total body clearance of levetiracetam when co-administered with enzyme-inducing anti-epileptic drugs (AEDs). Dose adjustment not necessary • 37.6% of pediatric patients reported behavioral symptoms compared to 13.3% in adults • Somnolence occurred in 22.8% in pediatric patients compared to 14.8% in adults • Information on dose, PK parameters, AE profile and clinical studies

Exclusivity Granted/ (Labeled)	Product	Labeled Indications Resulting from Pediatric Studies	Labeling Changes
1/29/03 (5/20/03)	Fentanyl Duragesic (Alza)	Chronic pain in opioid tolerant patients	• Safety evaluated in three open-label trials in 291 patients 2 years through 18 years of age with chronic pain • New Warning: Duragesic should be administered to children only if they are opioid-tolerant and age 2 years or older • New information on pharmacokinetics, dosage and administration and patient information • Precaution to guard against accidental ingestions by children • Adverse Events: no apparent pediatric-specific risk associated with Duragesic use in children as young as 2 years old when used as directed. Most common adverse events were fever (35%), vomiting (33%), and nausea (24%) Public Health Advisory 7/8/05-changes in boxed warnings/warnings, contraindications, precautions and dosage and administration emphasizing: • Use only in opioid tolerant patients with persistent pain-contraindication in the management of acute, mild or intermittent pain (e.g., prn), post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomy) and for short-treatment periods because serious or life-threatening hypoventilation could occur
10/28/04 (7/21/05)	Mixed salts Amphetamines Adderall XR (Shire)	ADHD	• Expanded labeling for 13-17 year olds • On a mg/kg body weight basis children 6-12 years have a higher clearance than adolescents or adults. Body weight is the primary determinant • There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit in a placebo-controlled study conducted in adolescents aged 13-17 with ADHD • In a single-dose PK study in adolescents, isolated increases in systolic blood pressure (SBP) were observed in patients receiving 10 mg and 20 mg Adderall XR. Higher single doses were associated with a greater increase in SBP • Sustained increases in blood pressure should be treated with dose reduction and/or appropriate medication • Information on dose, PK parameters, and AE profile
4/15/05 (8/11/05)	Meloxicam Mobic (Boehringer Ingelheim)	Relief of signs and symptoms of pauciarticular or polyarticular course juvenile rheumatoid arthritis	• Safety and efficacy established in patients 2 years of age and older • Clinical studies evaluated doses ranging from 0.125 mg/kg/day to 0.375 mg/kg/day. There was no additional benefit demonstrated by doses above 0.125 mg/kg/day in the clinical trials. The lowest effective dose should be used • Adverse events in children were similar to those in adults including skin reactions and gastrointestinal bleed risk • Information on dose, PK parameters, AE profile and clinical studies
5/24/05 (9/13/05)	Insulin aspart Recombinant Injection NovoLog (Novo Nordisk)	Diabetes mellitus	• In clinical studies comparing NovoLog to regular human insulin in patients 2 to 18 years with type 1 diabetes, NovoLog achieved glycemic control comparable to regular human insulin • The incidence of hypoglycemia was similar for both treatment groups
(9/28/05)	Emtricitabine – Emtriva (Gilead Sciences) Pediatric Formulation	Treatment of HIV-1 infection in combination with other antiretroviral agents	• Safety and effectiveness in pediatric patients 3 months and older supported by data from 3 open-label, nonrandomized clinical studies • Safety and effectiveness in patients <3 months have not been established • Relative bioavailability of Emtriva oral solution is approximately 80% of Emtriva capsules. Thus, maximum dosage is different for these 2 formulations: Solution max - 240 mg once daily; Capsules max - children weighing >33 kg one 200 mg capsule once daily • The AE profile in pediatric patients was comparable to that observed in adults • Information on dose, PK parameters, AE profile and clinical studies

Exclusivity Granted/ (Labeled)	Product	Labeled Indications Resulting from Pediatric Studies	Labeling Changes
6/14/05 (10/6/05)	Ritonavir Norvir (Abbott)	Treatment of HIV-infection in combination with other antiretroviral agents	• Extended age range from 2 years down to 1 month • AE profile in the pediatric population was similar to that for adults • Information on dose and PK parameters
3/2/05 (10/28/05)	Oxcarbazepine Trileptal (Novartis)	Use as adjunctive therapy in children aged 2 years and above with epilepsy	• Extended adjunctive therapy age range from 4 years down to 2 years • No evidence drug was effective as adjunctive therapy in patients <2 years • In clinical studies as adjunctive therapy, apparent clearance (L/hr/kg) decreased when age increased such that children 2 to <4 years of age may require up to twice the dose per body weight compared to adults; and children 4 to ≤12 years of age may require a 50% higher dose per body weight compared to adults • Approximately 11% of pediatric patients <4 years discontinued treatment because of adverse events including convulsions, status epilepticus and ataxia • Information on dose, PK parameters, AE profile and clinical studies
5/24/05 (11/28/05)	Glimepiride Amaryl (Aventis)		• Data are insufficient to recommend pediatric use of glimepiride • In an active-controlled, single-blind, 24-week trial, 272 pediatricpatients aged 8 to 17 years with Type 2 diabetes were randomized to treatment with glimepiride or metformin. Trial suggested differences favoring metformin • AE profile in the pediatric population was similar to that for adults • information on PK parameters
10/6/04 (12/8/05)	Sibutramine Meridia (Abbott)		• The data are inadequate to recommend the use of sibutramine for the treatment of obesity in pediatric patients • Efficacy in obese adolescents has not been adequately studied • Sibutramine's mechanism of action inhibiting the reuptake of serotonin and norepinephrine is similar to that of some antidepressants • It is unknown if sibutramine increases the risk of suicidal behavior or thinking in pediatric patients • In a study of adolescents with obesity in which 368 patients were treated with sibutramine and 130 patients with placebo, one patient in each group attempted suicide. Suicidal ideation was reported by 2 sibutramine-treated patients and none of the placebo patients
4/28/03 (12/21/05)	Alendronate Fosamax (Merck)		• Alendronate is not indicated for use in children • The efficacy and safety were examined in a randomized, double-blind, placebo-controlled two-year study of 139 patients, 4-18 years old, with severe osteogenesis imperfecta • Treatment with alendronate did not reduce the risk of fracture • There were no statistically significant differences between the alendronate and placebo groups in reduction of bone pain • Information on PK parameters, AE profile, and clinical studies
9/16/04 (3/16/06)	Irbesartan Avapro (Sanofi-Synthelabo)		• In a study at a dose up to 4.5 mg/kg once daily, irbesartan did not appear to lower blood pressure effectively in pediatric patients ages 6 to 16 years
12/15/05 (4/10/06)	Fluvastatin Lescol and Lescol XL (Novartis)	Heterozygous familial hypercholesterolemia as an adjunct to diet	• New indication in adolescent boys and girls (at least one year post-menarche) 10-16 years of age, with heterozygous familial hypercholesterolemia • Information on dose, AE profile and clinical studies

Exclusivity Granted/ (Labeled)	Product	Labeled Indications Resulting from Pediatric Studies	Labeling Changes
1/12/06 (5/10/06)	Octreotide Sandostatin LAR (Novartis)		• Efficacy and safety of octreotide as a weight loss agent were examined in a randomized double-blind, placebo-controlled study in 60 patients aged 6 –17 years with hypothalamic obesity from cranial insult; mean BMI increased 0.1 kg/m2 in drug treated patients compared to 0.0 kg/m2 in control-treated patients • No unexpected AEs were observed; however, the incidence of new cholelithiasis in this pediatric population (33%) was higher than that seen in adult indications • Information on PK parameters and AEs
6/9/06 (9/27/06)	Imatinib mesylate Gleevec (Novartis)	Treatment of newly diagnosed pediatric patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase	• Extended age range for the treatment of newly diagnosed CML down to pediatric patients • There are no data in children <2 years of age • Follow-up in children with newly diagnosed Ph+ chronic phase CML is limited • Information on hematologic toxicities, AE profile, clinical studies and dosing guidelines new for newly diagnosed pediatric patients
6/28/06 (9/28/06)	Brinzolamide Azopt ophthalmic suspension (Alcon)		• IOP-lowering efficacy was not demonstrated in a 3-month controlled clinical study in which brinzolamide was dosed only twice a day in pediatric patients 4 weeks to 5 years of age
6/28/06 (9/28/06)	Levobetaxolol Betaxon ophthalmic suspension (Alcon)	Treatment of elevated intraocular pressure	• Extended indication from adults to pediatric patients • The adverse event profile was comparable to that seen in adults and elderly patients
(9/29/06)	Enfuvirtide Fuzeon (Hoffmann-La Roche)	Treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy	• Additional safety and efficacy data and AE information from clinical study in 5-16 year olds • Insufficient data to provide dosing recommendations in patients <6 years

Note: These labeling changes only reflect the pediatric changes for studies submitted in response to a written request and are not necessarily the most current label. More current labeling can be found at www.drugs@FDA.gov.

Mr. PALLONE. Thank you. Dr. Lurie.

STATEMENT OF PETER LURIE, M.D., M.P.H., DEPUTY DIRECTOR, PUBLIC CITIZEN'S HEALTH RESEARCH GROUP

Mr. LURIE. Good morning, and thank you for the opportunity to testify before the committee. You have already heard a lot about the successes of the Act, and I think that they are clear and don't merit challenge exactly, but those aren't the right questions. The right questions are firstly whether or not the system could be more successful and second, whether or not these successes or perhaps even greater ones could have been obtained through an alternative method, and I will address those two questions in turn.

First, are there gaps, and I think there are three. We have heard some of them from Dr. Crosse on off-patent, on-patent, and I will talk especially about the diseases that have been studied.

The biggest deficiency is in off-patent drug studies, and I don't think that is a surprise to anybody given the way the BPCA is structured. As Dr. Crosse testified, very few of the off-patent drugs for which studies have been requested have in fact been done. In 83 percent of the studies requested by the NIH, no study has been done. So I think we are looking at a significant problem there. In part this is because the NIH has received no appropriations specifically for these pediatric studies. And even with respect to on-patent drugs, there are problems as well. According to the GAO, 19 percent of written requests from the FDA were turned down, presumably because there wasn't enough money to be made from conducting studies; and the BPCA does provide a mechanism for the study of those written requests that have been declined, but as we have heard in the end not one of those studies has in fact been funded. So those are the first two points.

The third is that the kinds of diseases being studied are, not surprisingly, those diseases that are likely to have large sales in adults because that is where the great majority of the pharmaceutical market is. So market-based solutions result in these kinds of market-based distortions. Using two different data sources, GAO determined that only four or five, depending on which data source you looked at, of the 10 most commonly prescribed pediatric drugs had in fact been studied under the BPCA. And a group of researchers in the Netherlands which has just implemented a BPCA-like solution of its own has studied the United States experience, and what they found was that the profile of drugs being studied much more closely mirrored in the adult population prescribing habits than it did in the pediatric. For example, the top three drug categories that were granted pediatric exclusivity matched precisely in both category and sequence the top three prescribing categories for adults and none of the three top-prescribing categories for children appeared in the top three for which pediatric exclusivity was granted. So we have a clear distortion there.

So, first, it is not really working as well as some people have said, and second, my point is that there are other ways of receiving these exact benefits without the kinds of handouts to industry that have so far characterized this initiative. And of course, the obvious model here is the PREA which has already produced 55 labeling changes, all of these of course without any need to resort to a pat-

ent extension. Recent published research shows the exclusivity provisions under the BPCA can be absurdly generous. Nine drugs were studied, and for the current 6-month patent extension, the net economic returns on individual drugs were as high as $508 million with a median of $134 million. For one drug product with $3.8 billion in sales, the economic benefit to the sponsor was 74 times as high as its expenses, a 7,400 percent profit margin, and the median was a 12.4 times net gain for the companies.

And the costs of this are substantial. As mentioned earlier by Ms. Schakowsky, the FDA estimated in 2001 that the total value of the 6-month patent extension would be on the order of $13.9 billion. Much of this will come out of the pockets of consumers but now with Medicare Part D, the Government will be footing the bill for its own generosity as well. Unless there is a strong reason to believe that pediatric use will be minimal, conducting pediatric studies should be seen as the responsibility of all companies seeking to market or to continue marketing a drug, not an undertaking for which companies should be rewarded, let alone as generously as they currently are. The FDA should have the authority to compel such studies by expanding the provisions of PREA no matter what the stage in the drug's lifespan without having to resort to patent extensions.

I mentioned in my written testimony that the pediatric testing process is not transparent, and I shan't go into that in detail, just to mention briefly that the FDA does not make clear when the studies are actually being conducted and when they might be completed. There are delays in label changes of the order of time that we have heard, and in addition, if you think that doctors can instead rely upon published medical literature as a substitute while they are waiting for the label change to actually take place, that is not the case because in many cases, particularly if the result is negative, the companies don't bother to publish.

Let me just make a couple of brief comments on medical devices which are general comments but apply in the pediatric situation as well. First, the medical device approval standard is too low. To receive permission for a device to be approved, the standard is that there must be, quote, "reasonable assurance that the device is safe and effective", a much lower standard than for drugs where the standard is "substantial evidence of effectiveness for the claimed conditions." So the result is we can see, with otherwise equal data, a device being approved where a drug would not, and that is potentially diverting people from effective drugs to less effective or ineffective devices. The vagus nerve stimulator is a good example of this, and in that particular case the people from the drug division of the FDA told the Senate finance committee that had data of that quality been submitted to them, they would not even have permitted the filing of a new drug application, instead, the device wound up being approved.

A second problem involves the 510(k) process which in effect is a less-than-full pre-market review for most devices including most class 3 devices which are the most invasive of those class 3 devices. Intended at the time of the enactment of the amendments to be the exception rather than the rule, a 510(k) is now the route to approval for 99 percent of new class 3 devices. Moreover, a device can

be considered substantially equivalent under the 510(k) through a predicate device, the already approved device, even if it does not have the same technological characteristics as the predicate device. A recent example of this is something called Repetitive Transcranial Magnetic Stimulation, rTMS system, in which even though the predicate device, electroshock therapy, electricity, this device was considered for approval under 510(k) as being substantially equivalent, even though it used magnets. This makes no sense at all and makes it far too easy for devices to get on the market without proper approval.

In parallel to the situation under drugs, the medical device testing process is also not transparent; and the Institute of Medicine's report on that makes it quite clear. Quote, "the most obvious deficits in FDA's performance are the lack of effective procedures for monitoring the status of required post-market studies and the lack of public information regarding such studies." In that respect as well, we need to see an improvement in transparency.

That is the end of my comments.

[The prepared statement of Dr. Lurie follows:]

Peter Lurie, MD, MPH
Deputy Director, Public Citizen's Health Research Group
Testimony before the Health Subcommittee
Committee on Energy and Commerce
U.S. House of Representatives
on Programs Affecting Safety and Innovation in Pediatric Therapies
May 22, 2007

Thank you for the opportunity to address the Subcommittee on the critical issue of the safety and effectiveness of pediatric therapies. My comments today will address two principal areas: a. how to ensure that the most important studies of pediatric drugs and biologics are indeed conducted; and b. issues surrounding the approval of medical devices, including for children.

A. Pediatric Studies

Much of the testimony you heard this morning will have extolled the successes of the current system for encouraging pediatric studies of drugs and biologics. To simplify somewhat, the system consists of a carrot and a stick. The carrot is the Best Pharmaceuticals for Children Act (BPCA) of 2002,[1] which grants six additional months of marketing exclusivity to companies that conduct pediatric studies consistent with a Written Request issued by the Food and Drug Administration (FDA). The stick is a codification of an FDA regulation known as the Pediatric Rule,[2] which was successfully challenged in the courts; that ruling was later appealed. With the fate of the Pediatric

[1] BPCA was actually a successor to the exclusivity provisions in the Food and Drug Modernization Act of 1997.
[2] 63 Fed Reg 66632, December 2, 1998.

Rule unclear, Congress in 2003 passed the largely similar Pediatric Research Equity Act (PREA) which contains the essential elements of the Pediatric Rule: the ability of the FDA to require pediatric studies whenever a sponsor seeks approval for a new ingredient, indication, dosage form, dosing regimen or route of administration.

The successes of the present system are clear enough. They include, as of May 2005, 299 Written Requests under the BPCA, many of which would never have taken place without the Act, 110 patent extensions and 90 labeling changes.[3] (The number of drugs relabeled has since risen to 128.[4]) Yet, the question is not simply whether the system has had successes. That much is undeniable. Rather, the issues are, first, whether the system could have been more successful and, second, whether these successes (or even greater successes) could have been obtained through alternate methods. Let us take these issues in turn.

There remain numerous gaps in current pediatric testing

While many studies have been undertaken, significant gaps remain. The biggest deficiency is with drugs that are off patent, an observation that should surprise no-one. Tellingly, the data on off-patent drugs in the Government Accountability Office's (GAO's) report[5] on the BPCA have been relegated to an appendix.[6] But the results are

[3] Mathis D. Pediatric drug development: BPCA and PREA. Presentation before the Drug Information Association. Division of Pediatric Drug Development, U.S. Food and Drug Administration, June 28, 2005. Available at: http://www.fda.gov/cder/present/DIA2005/mathis.pdf.
[4] http://www.fda.gov/cder/pediatric/labelchange.htm.
[5] Government Accountability Office. Pediatric drug research: studies conducted under Best Pharmaceuticals for Children Act. GAO-07-557, March 2007.
[6] The PREA has little impact upon off-patent drugs.

disconcerting. Following the process outlined under the BPCA, the National Institutes of Health (NIH) had by 2005 identified 40 off-patent drugs for which pediatric studies would have been useful. Yet the FDA issued Written Requests for only 16 of these and the drugs' sponsors declined to conduct all but one of them. While the NIH had funded studies of seven of the remaining 15, that still left the great majority (83%) of the NIH's list unstudied. In part, this is because the NIH has received no appropriations specifically for these pediatric studies.

Even with respect to on-patent drugs, significant deficiencies remain. According to the GAO, between 2002 and 2005 sponsors declined 41 of 214 (19%) Written Requests from the FDA, presumably because they did not think it was in their financial interest to conduct the requested studies. This is an underestimate of the extent to which companies are not complying with the FDA's priorities in that many of the Written Requests are generated at the urging of the sponsor; presumably these are not being declined. The BPCA does provide a mechanism for the study of drugs for which Written Requests have been declined: the FDA can refer such studies to the Foundation for the National Institutes of Health (FNIH). This mechanism has been an abject failure. Of the 41 declined Written Requests, the FDA referred only nine to the FNIH, which in turn had funded none.

The third area of deficiency relates to the kinds of diseases being studied. Since the majority of sales for most drugs will be derived from adult sales, fundamental economic principles predict that companies would undertake pediatric studies (and thus expect

exclusivity under the BPCA) in relation not to their pediatric sales, but to their adult sales. Using two different data sources, the GAO determined that only four or five of the 10 most commonly prescribed pediatric drugs had been studied under the BPCA.[5] The FDA acknowledged in its report to Congress in 2001 that the BPCA was inadequate for old antibiotics and other off-patent drugs, certain drugs with low sales and for the younger pediatric age groups.[7]

A group of researchers in the Netherlands, where a European law similar to the BPCA comes into effect this year, has studied the U.S. experience.[8] They found that the diseases for which drugs were most frequently granted pediatric exclusivity treated depression and mood disorders, hypertension, elevated cholesterol, HIV and pain, common conditions in adults. The top three drug categories granted pediatric exclusivity precisely matched (in category and sequence) the top three prescribing categories for adults, while none of the top three prescribing categories for children appeared in the top three for the granting of pediatric exclusivity. In general, the researchers concluded, "The distribution of the different drugs closely matched the distribution of these drugs over the adult market, and not the drug utilization by children."

The fact that the primary motivation for studying pediatric patients is, in many instances, sales in adults raises significant ethical questions. Because the primary beneficiaries of such studies are often pharmaceutical companies rather than the study participants or the

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[7] Department of Health and Human Services, U.S. Food and Drug Administration. The pediatric exclusivity provision: report to Congress. January 2001. Available at: http://www.fda.gov/cder/pediatric/reportcong01.pdf.

[8] Boots I, Sukhai RN, Klein RH, et al. Stimulation programs for pediatric drug research – do children really benefit? European Journal of Pediatrics, January 17, 2007.

pediatric population from which the participants are drawn, Institutional Review Boards should compensate for this dynamic by lowering the amount of acceptable risk for these pediatric patients. Moreover, patients and their surrogates have a right to be fully apprised of the financial arrangements that underly the research.[9]

With significant deficiencies in the study of both off- and on-patent drugs, and a profile of studies that leaves many important pediatric conditions neglected, it is clear that, whatever its successes, the current system is far from perfect.

The successes of the current program can be retained without such massive handouts to industry

The second major question is whether the successes of today's system could be realized through other means. Specifically, are the current patent extensions too generous or, more fundamentally, are they needed at all? Here we turn to the PREA, the exemplar of the stick approach to this issue.

Although only enacted in December 2003, the PREA has already produced 55 changes in drug labels. Like the labeling changes under the BPCA, these changes have ranged from new indications to proof of ineffectiveness in certain subgroups to better descriptions of the drug's adverse event profile in the pediatric population. All of these benefits were obtained without the patent extensions that are at the core of the BPCA.

[9] For a fuller discussion of these issues, see Lurie P. Statement before the National Academy of Sciences' Committee on Clinical Research Involving Children, July 9, 2003. Available at: http://www.citizen.org/publications/print_release.cfm?ID=7261.

Recently published research[10] indicates that the exclusivity provisions under the BPCA are absurdly generous, at least for some drugs. The authors studied nine drugs from a variety of disease categories to determine whether the value of patent extensions exceeded the costs of conducting the supporting pediatric trials. For the current six-month patent extension, the net economic returns on individual drugs were as high as $508 million, with a median of $134 million. Only one drug did not produce a net financial gain, a loss of $8.9 million on $28.3 million in annual sales. One drug product, with $3.8 billion in annual sales, produced economic benefits to the sponsor 74 times as high as its expenses (median for all drugs: 12.4 times). Even with the patent extension reduced to three months, only one company had expenditures that would have exceeded the value of the added exclusivity (median for all drugs: 5.7 times greater returns than costs). The version of PDUFA recently passed in the Senate[11] reduces the patent extension to three months for drugs with sales exceeding $1 billion in any year prior to the time the sponsor agrees to the Written Request. This is a move in the right direction, but still seems too generous.

The costs of this generosity are substantial. The FDA estimated in 2001 that the undiscounted value of the six-month patent extensions would be $13.9 billion over the following 20 years. Much of this will come out of the pockets of consumers, but increasingly the government will be footing the bill for its own generosity, in the form of its contribution to funding Medicare Part D.

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[10] Li JS, Eisenstein EL, Grabowski HG, et al. Economic return of clinical trials performed under the pediatric exclusivity program. Journal of the American Medical Association 2007;297:480-8.
[11] http://thomas.loc.gov. Search on S. 1082.

Unless there is a strong reason to believe that pediatric usage will be minimal, conducting pediatric studies should be seen as the responsibility of all companies seeking to market or continue marketing a drug, not an undertaking for which companies should be rewarded, let alone as generously as they currently are. The FDA should have the authority to compel such studies, by expanding the provisions of the PREA, no matter what the stage in the drug's lifespan, without having to resort to patent extensions. This authority would extent to old and new drugs, to on-patent and off-patent drugs.

The pediatric testing process is not transparent

In addition to ending the excesses of the patent extension provisions, Congress should pay attention to the lack of transparency in the process. The FDA does not announce which products are being studied pursuant to Written Requests and generic companies have been forced to destroy drug lots after they learned at the last minute that a patent extension would be granted.[5] In addition, there can be a significant delay between initial submission of the pediatric trial results and any label change that may result. For drugs granted pediatric exclusivity between 2002 and 2005 that resulted in a label change, that change took place eight months or more after the data were originally submitted to the FDA in 40% of cases and over a year later in 16% of cases.[5] Inadequacies in the data submitted by the sponsors and the FDA's lack of authority to dictate label changes help explain these delays.

Although many products have been relabeled as a result of pediatric trials under the PREA and the BPCA, many physicians do not read these FDA-approved labels on a regular basis. The published medical literature is not a satisfactory substitute as only 45% of BPCA studies completed between 1998 and 2004 were published.[12] Studies were more likely to be published if they addressed questions of efficacy or if the labeling changes were favorable to the product. Congress should require a clinical trials registry that would publicize the existence and design of all pediatric studies that have commenced and the detailed results of those that have been completed.

B. Medical Devices

The issues with respect to pediatric medical devices are generally similar to those raised for pediatric drugs (lack of studies, devices too large for children, improper extrapolation from adult studies, etc.). Yet medical device regulation raises a number of specific issues, all of which apply equally to adult and pediatric devices.

The medical device approval standard is too low

The first problem is that the approval standard for devices that treat diseases is lower than that for drugs. Thus, to receive permission to be marketed, a drug must demonstrate "substantial evidence of effectiveness for the claimed indications,"[13] whereas a device

[12] Benjamin DK, Smith PB, Murphy D, et al. Peer-reviewed publication of clinical trials completed for pediatric exclusivity. Journal of the American Medical Asssociation 2006;296:1266-73.
[13] 21 CFR 314.50(d)(5)(v).

need only demonstrate a "reasonable assurance that the device is safe and effective."[14] Thus data that could never support the approval of a drug can result in the approval of a device used to treat the same condition, potentially diverting patients from effective drugs to devices. This is not a merely theoretical concern. The vagus nerve stimulator was approved in 2005 by the Center for Devices and Radiological Health (CDRH) for treatment-resistant depression even though the only randomized, controlled trial of the device did not demonstrate efficacy. According to a report from the Senate Finance Committee,[15] officials in the Center for Drug Evaluation and Research advised CDRH that if it had received similar data for an antidepressant drug, it would not have sanctioned even the filing of a New Drug Application (NDA). Yet the device was approved.

Most devices do not undergo full premarket review

A second major issue is the abuse of the 510(k) process for Class III medical devices. The Medical Device Amendments of 1976 allow two pathways to approval for such devices: a Premarket Application (PMA), analogous to the NDA for drugs, and the 510(k) process, in which new devices are approved based on their "substantial equivalence" to an existing (predicate) device. Intended at the time of the enactment of the amendments to be the exception, rather than the rule, the 510(k) process is now the

[14] 21 CFR 860.7(4)(c)(1).
[15] Committee on Finance, United States Senate. Review of the FDA's approval process for the vagus nerve stimulation therapy system for treatment-resistant depression. February 2006. Available at: http://finance.senate.gov/press/Gpress/02_2006%20report.pdf.

route to approval for 99% of new Class III devices,[16] resulting in a less rigorous approval process, including no ability to require advisory committee meetings. Moreover, a device can be declared "substantially equivalent" to the predicate device even if it does not have the same technological characteristics as the predicate device as long as it "does not raise new questions of safety and effectiveness and demonstrates that the device is at least as safe and effective as the legally marketed device."[17]

The dangers of this loophole, derived directly from the statute, are graphically illustrated by another device for the treatment of depression, Repetitive Transcranial Magnetic Stimulation (rTMS). The FDA allowed this new device to be reviewed under the 510(k) process with electroconvulsive therapy (ECT) as the predicate device, even though ECT uses electrical currents and rTMS applies a magnetic field. Remarkably, the company then compared rTMS to a placebo, even though ECT was the predicate device. Ironically this study, which is the only randomized, controlled trial of rTMS, did not prove that the device was more effective than a placebo. At this time, it appears unlikely that rTMS will be approved.

Devices known to be defective continue to be marketed even after the defect is corrected

Third, at times when the FDA has identified or been apprised of a defect in an already marketed device, it has allowed the sponsor to correct the defect but to continue to deplete its inventory of the device it acknowledged to be defective. The best known

[16] Riegel v. Medtronic, Inc., 451 F.3d 104, 111-12 & n.7 (2d Cir. 2006).
[17] http://www.fda.gov/cdrh/devadvice/314.html.

example of this involved the Guidant pacemakers,[18,19] but we have brought another such case to light.[20] In this instance, a patient had his St. Jude pacemaker removed due to a short-circuit that depleted the battery. However, when his new pacemaker was implanted, he received one from a group of pacemakers that still could carry the defect, even though the company was already selling a new pacemaker with the defect corrected. Fortunately, his new pacemaker has not failed.

The medical device testing process is not transparent

Fourth, as with pediatric drug and biologic studies, there are a number of respects in which procedures regarding devices are less than transparent. According to a report from the National Academy of Sciences (NAS), "The most obvious deficits in FDA's performance [with respect to the safety of medical devices in children] are the agency's lack of effective procedures for monitoring the status of required postmarket studies and the lack of public information regarding such studies."[21] The report went on to recommend expanded FDA authority to order postmarketing studies as well as a public registry that would track all postmarketing studies on medical devices. These elements are included in H.R. 1494, the Pediatric Medical Device Safety and Improvement Act, which goes beyond the NAS recommendations to also require the posting of study results but, unfortunately, allows non-disclosure of results if the sponsor provides "an

[18] Meier B. Maker of heart device kept flaw from doctors. New York Times, May 24, 2005, p. A1.
[19] Meier B. Heart device sold despite flaw, data shows. New York Times, June 2, 2005.
[20] http://www.citizen.org/publications/release.cfm?ID=7401.
[21] Field MJ, Tilson H, eds. Safe Medical Devices for Children. Committee on Postmarket Surveillance of Pediatric Medical Devices, Institute of Medicine, 2005.

explanation as to why the results and key findings do not warrant public availability."[22] This loophole is not justifiable.

I would be happy to address any questions members of the committee may have.

[22] http://thomas.loc.gov. Search on H.R. 1494.

Summary of Major Points

A. Pediatric Studies

1. There remain numerous gaps in current pediatric testing

    Off-patent drugs

    Certain on-patent drugs

    Certain conditions

2. The successes of the current program can be retained without such massive handouts to industry

3. The pediatric testing process is not transparent

B. Medical Devices

1. The medical device approval standard is too low

2. Most devices do not undergo full premarket review

3. Devices known to be defective continue to be marketed even after the defect is corrected

4. The medical device testing process is not transparent

Mr. PALLONE. Thank you. I have been letting some of you go beyond 2 minutes only because I am interested in what you are saying, but we can't be going too long. Let me go next to Ms. Belfiore. Thank you.

STATEMENT OF SUSAN BELFIORE, PRINCETON, NJ

Ms. BELFIORE. Thank you. Mr. Chairman, Ranking Member Deal, and distinguished committee members, thank you so much for having me here today. I am Susan Belfiore. I am the mother of five children. Four of those five children, my husband and I adopted from Romania, and they are HIV-positive.

I am honored to be here today to let you know the difference that the pediatric drug legislation has made in our lives and why it is so important to continue to test drugs specifically for children. This issue is not settled by any means, but the progress we are making is because of you. You are all true champions for children. I would like to give a special thanks to Ms. Eshoo and Mr. Waxman for their longstanding leadership on this issue. My children would like to be here today. They have lobbied hard to be here today to thank you personally, but alas, they have finals.

I would last like to thank the Elizabeth Glaser Pediatric AIDS Foundation for the work they do for children and families. Our children are living healthier, better lives because of their work.

I am here today because our family, like so many families throughout the country, are dependent on medications to keep their children strong and healthy. As you just heard, four of our five children have the AIDS virus. Our daughters, Mihaela and Loredana, are taking live-sustaining drugs. So clearly this is an issue that is close to my heart. As a parent, there is nothing more difficult than knowing that your child is sick. You can often feel scared and helpless, yet our family believes in miracles but miracles cannot happen without the 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 Mihaela on a cocktail of drugs that was used by many adult AIDS patients. We took the medications out of the pill boxes, put it in a special box that was decorated with horses. Mihaela loves horses, and we had a silly hat party that night at the dining 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 will be dependent on the latest medications to keep her healthy. But the truth is that Loredana and thousands of children like them are dependent on the latest medications to keep them strong, healthy, 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, our children won't have a chance. They cannot rely on guesswork. We tried that, and I can tell you, it does not work.

This binder here contains my children's medical life for the last 14 years. I have cataloged all aspects of their health, every 3 months, blood work being done, medications that they were taking, any adverse effects to the medication, and illnesses.

Ten years ago we thought Mihaela was taking an effective drug regime for HIV. She was not. It turns out she had been under

medicated because the drug she was taking had not been studied sufficiently 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. It means that your child has lost access to one drug regime in a very limited supply of options, and when options run out, children suffer.

I recently looked at a picture of Mihaela from 5 years ago when we first came to Congress to advocate for the Pediatric Research Equity Act. I was shocked when I saw the picture of her standing there that day. She was underweight, she had a look about her that you might know as being very familiar with the AIDS virus, more advanced stages of the AIDS virus. She had failure to thrive. When I was in that moment, I didn't realize it. I didn't realize it until I went back and I looked at that photo.

In the last 5 years, though, things are very 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, and she is free of infections. And for the last 4 years, Mihaela has had undetectable virus in her system. She now 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 my individual family. My family and I are here for all parents today. You have heard the statistics, about three-quarters of all medication has not been tested for use in children. The drugs are from everything from asthma, cancer, to HIV and AIDS.

Now, I understand that testing for drugs for use in children is an additional expense for the drug companies. I also understand it can be difficult to conduct studies for a variety of enrollment issues. That is why BPCA includes an incentive for companies to do pediatric studies. The law is working well and it should be continued.

But this issue is not just about profits and 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 use in children should even be a question. As a adults we wouldn't take medication that is not tested for us, so why would we give it to our children. That is why I strongly believe the Pediatric Research Equity Act should be made permanent.

I appeal to you on behalf of my children and millions of children like them. Surely we can agree that our children deserve nothing less than the same information about safety and dosing that we require of ourselves.

Thank you again for inviting me here today, and on behalf of all parents, thank you so much for what you are doing for our children. I can tell you personally, it really is making a difference.

[The prepared statement of Ms. Belfiore follows:]

STATEMENT OF SUSAN BELFIORE

Mr. Chairman, Ranking Member Deal and distinguished committee members. Thank you so much for having me here today. I am Susan Belfiore, mother of 5 chil-

dren, 4 of whom are HIV positive. I'm honored to be here today to let you know the difference pediatric drug legislation 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.

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 am 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 can often feel scared and helpless. 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 eight-year-old daughter Mihaela on a 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 healthy.

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, many 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. For the last 14 years, I have cataloged all aspects of their health. Charting their blood work every three months, their medications, and their reactions to these medications.

Ten 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.

Recently I looked at a picture of Mihaela from 5 years ago when we first came to Congress to advocate for the Pediatric Research Equity Act to become law. 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 the last five 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. She now rides horses more than ever.

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. My family and I are here for all parents and 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 to cancer to HIV and AIDS.

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.

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.

I appeal to you on behalf of my children, 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.

Mr. PALLONE. Thank you so much, and thank you for being here today to tell the story. I appreciate it. Mr. Rozynski.

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

Mr. ROZYNSKI. Good afternoon, Chairman Pallone, Ranking Member Deal, and other members of the subcommittee. Mr. Burgess, thank you for your comments.

Again, my name is Ed Rozynski from the Stryker Corporation. As an early supporter of the bill, we sincerely appreciate Congressmen Markey and Rogers' 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, and is headquartered in Kalamazoo, MI. Stryker also has facilities in New Jersey, Massachusetts, California, Texas, New Hampshire, and Tennessee. Stryker's products are used in over 80 percent of the hip and knee replacement procedures performed in the United States. Currently our bone healing and bone regeneration technology is being used for humanitarian purposes to save the limbs and to repair the backs of soldiers at Walter Reed Hospital.

Stryker's commitment to children is not new. We are the leading manufacturer of orthopedic oncology prostheses and pediatric-related devices used to treat cranial facial deformities such as cleft lip and palate. Soft tissue sarcomas 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 primary malignant bone and soft tissue sarcoma was amputation. Since that time, Stryker has developed limb-sparing solutions including a growing prosthesis that can be elongated to account for a child's growth. With respect to cranial facial deformities, Stryker partners with medical organizations such as Operation Smile, a non-profit organization which last year was able to provide free cleft lip surgeries to more than 8,000 children in 23 countries, on average taking 45 minutes and costing just $242 per child. These surgeries have a positive, lasting impact on the lives of children and their families.

It is our sincere hope that this pediatric device legislation will encourage the evolution of novel healthcare solutions for children. First, the bill authorizes new money to create a grant program to promote pediatric device development including matchmaking between inventors and manufacturers. Second, the bill improves incentives to develop devices for the pediatric device market which is very small, and I would want to underscore very small with respect to pediatric devices. These incentives at least directionally should entice companies to think about developing pediatric prod-

ucts that they might otherwise have neglected in favor of profitable products developed for use in the much larger adult population.

Third, the bill facilitates the pooling and collection of more information about pediatric devices so that information and solutions can be easily shared and analyzed within the community.

We are aware of ongoing discussions related to the post-market surveillance provisions of the bill and hope successful resolution will be reached on this issue. This bill has twin goals which together must be achieved, number one, bringing more pediatric devices to market and number two, improving information about pediatric devices. All stakeholders should work together to ensure that both goals are achieved.

In conclusion, Chairman Pallone and members of the committee, we applaud you for considering 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 gadgets. Therefore, we should not allow children's healthcare products to become the residual of products that we develop for the big people that they look up to. Children deserve our special attention, children deserve our very best efforts. 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 children, their sick child to a faraway hospital. Stryker will soon announce a plan to provide charitable assistance to families and patients to cover their expenses associated with travel to NIH Cancer Care Centers, expenses not covered by health insurance. These uncovered expenses often pose a serious impediment to a family's ability to provide for their child's care and recovery. We believe that Stryker's charitable initiative will compliment the advanced technologies for children that Stryker already develops. It is our hope that we and other medical technologies will be further encouraged to develop more pediatric devices as a result of this legislation.

Again, thank you, Mr. Chairman. I would be pleased to answer any questions the committee may have.

[The prepared statement of Mr. Rozynski follows:]

TESTIMONY OF ED ROZYNSKI
VICE PRESIDENT, GLOBAL GOVERNMENT AFFAIRS
STRYKER CORPORATION

U.S. HOUSE OF REPRESENTATIVES ENERGY AND COMMERCE COMMITTEE
SUBCOMMITEE ON HEALTH
"Programs Affecting Safety and Innovation in Pediatric Therapies"
Tuesday, May 22, 2007 – 10:00 am
Room 2322, Rayburn House Office Building

Introduction

Good morning. Chairman Pallone, Ranking Member Deal, and Members of the Subcommittee, my name is Ed Rozynski. I am Vice President of Global Government Affairs for Stryker Corporation ("Stryker"). On behalf of Stryker, I am pleased to present testimony today in support of the "Pediatric Medical Device Safety and Improvement Act of 2007" (H.R. 1494), which would promote the development of medical technologies for children.

As an early supporter of the bill, we sincerely appreciate Congressmen Markey and Rogers' 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.

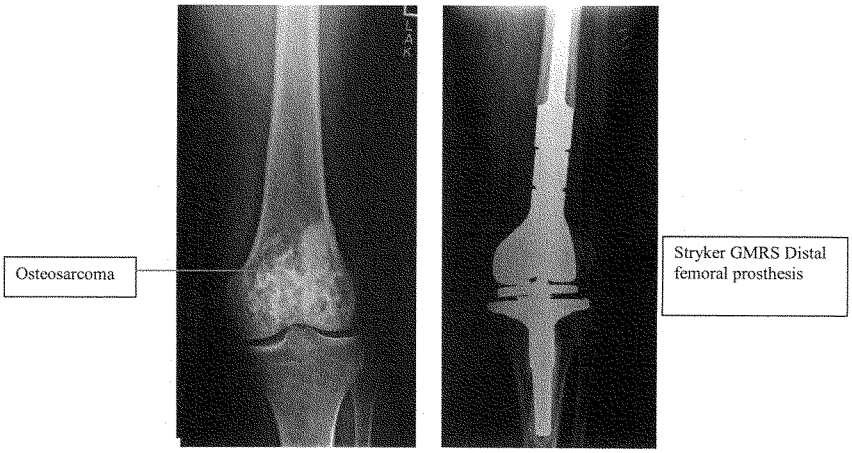
Stryker's commitment to children is not new. Our company is a market leader in products of significance for children. We are the leading manufacturer of orthopaedic oncology prostheses in the United States and have a significant presence in other medical specialties with a high percentage of pediatric 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 would 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 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 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 form premature fusion of the sutures or connections of the skull bones and has been estimated as a problem in three 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 reabsorbable plates and screws specifically designed to reabsorb 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 new pediatric products only while maintaining the cap of 4,000, in an effort to encourage more manufacturers to pursue the development of these products serving such small numbers of children.

Improving the incentives for pediatric HDE products 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 and turn them into a reality for young patients.

Third, the bill facilitates the pooling and collection of more information about pediatric devices. It requires companies and other researchers to place certain pediatric postmarket studies and 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. We are aware of ongoing discussions related to the postmarket surveillance provisions of the bill and hope successful resolution will be reached on this issue. This bill has twin goals that we support: bringing more pediatric medical devices to market and improving information about pediatric devices. All stakeholders should work together to ensure that provisions of this bill are structured so that both goals may be achieved.

We applaud Congressmen Markey and Rogers for introducing this bill, and we thank all of the Members of the Subcommittee for considering this important legislation. We 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. For example, we see the hope and the benefit that our latest bone implants provide to children with cancerous tumors.

Additionally, in an effort to reach even more children, Stryker has decided that we will 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 travel, lodging, and other non-healthcare 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.

We believe that Stryker's charitable initiative will complement the advanced medical technologies for children that Stryker already develops and manufactures. It is our hope that we and other medical device companies will be further encouraged to develop more pediatric devices as a result of Congressmen Markey and Rogers' legislation.

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

Mr. PALLONE. Thank you, Mr. Rozynski. Mr. Lombardi.

STATEMENT OF DONALD P. LOMBARDI, PRESIDENT AND CEO, INSTITUTE FOR PEDIATRIC INNOVATION

Mr. LOMBARDI. Thank you, Mr. Chairman and committee members. While a lot of the testimony has focused on how to research, test, and regulate pediatric products, I would like also to ask that Congress think about what it can do to stimulate the invention and development of products that have the special requirements needed for treating children.

My name is Don Lombardi. I am president and CEO of the Institute for Pediatric Innovation, a non-profit organization located in Cambridge Massachusetts.

The challenges that industry faces in getting products developed for children are also faced by pediatric hospitals in their attempts to commercialize discoveries they make. I was the chief intellectual property officer for Children's Hospital Boston for 15 years, responsible for managing that organization's compliance with the Bayh-Dole Act which focuses on the translation of research discoveries to commercial products for the benefit of the public. The program was very successful. Six products got onto the market, 10 more into clinical development through our licensee companies. Twenty-five new companies were started around our technologies. The program brought in tens of millions of dollars of license revenues to Children's Hospital.

The paradox? Very little of these products benefited children. Most were based on very early stage biology research, and the investors and companies who took on these ideas to develop them naturally focused on the largest and easiest to access adult markets. My experience at Children's Hospital Boston is reflected as well in the experience of the major pediatric hospitals everywhere.

You have heard a lot about the issues of the small market size and the challenging regulatory pathways and the fact that children aren't small adults. I won't reiterate those issues. I would like to add another perspective based on the experience in the tech transfer program at an academic institution such as these pediatric hospitals. The innovation process focuses on researchers, not on clinicians. Clinicians are the ones who know what is needed, not the researchers. On the other hand, the clinicians generally lack the time and the ability to create inventions and develop products. This problem is a national-scale problem that needs novel approaches to collaborations between the hospitals and industry and between these parties and others who can provide pieces of the puzzle to develop products.

I left my job at Children's Hospital Boston a year ago to create the Institute for Pediatric Innovation to focus exclusively on the practical translation of ideas into products for pediatric care.

Our plan is to form a small consortium of leading pediatric centers, and using this consortium as a microcosm of the market, carry out a very careful needs analysis to determine what products are needed to save lives, improve outcomes, reduce costs, increase satisfaction of patients, parents, and caregivers. We will then evaluate and set priorities on the products based on three criteria, first, which ones will have the highest impact; second, of these, which

are commercially feasible; and third, of these, which can our specific consortium members add value both in the product design and the clinical testing phase. From these we will select six or seven products and develop detailed opportunity analyses of these products. We are going to focus initially on three categories of products. The first is reformulated drugs. You have heard from other testimony about the off-label use of drugs. I have learned in an informal survey of five or six pediatric hospitals that some 60 percent of the prescriptions written in institutions such as these are actually formulated off label by the pharmacies in the hospital, which is an enormous of risk for patients and institutions themselves. And I know from my conversations with these parties that there are somewhere between 30 and 50 pharmaceuticals that pediatricians either do use or wish to use that are not available in the proper dosage and delivery forms.

The second area is in the re-engineering of medical devices. Again, as you have been told, this is not just downsizing devices. There are a variety of specific pediatric bioengineering issues that need to be addressed in the redesign and the re-engineering of these products. These products need to adapt to the very different physiology, material interactions with the body, impact on the patient's skin and of course the very challenging issue of the dynamic nature of both the anatomy and the physiology of the child.

Following this we will undertake what we call product imagination, brainstorming sessions that will bring together nurses, doctors, engineers and marketing people to imagine and develop product concepts for new products. For the new products as opposed to the re-engineered and reformulated projects we are focusing initially on the needs of neonatal care. This is because we have a company which has agreed to fund this program. We expect that the practices that we develop for developing new products we can also apply in other areas with other companies in general pediatric surgery, cardiology, GI, and neurosurgery. Finally, I congratulate the committee for its work in this area, and my recommendations about legislation are included in my handout. Thank you very much.

[The prepared statement of Mr. Lombardi follows:]

U.S. House Committee on Energy and Commerce
Subcommittee on Health

Hearing on Programs Affecting Safety
and Innovation in Pediatric Therapies

May 22, 2007

Submitted for the Record

By

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Key Points

1. Standard approaches for commercializing innovations don't work for pediatrics, including the system for transferring Federally funded research results from academic and medical research institutions to the for profit sector as contemplated under the Bayh Dole Act of 1980.

2. A solution requires novel forms of public-private, nonprofit-for profit collaboration to carefully assess what products are needed and to drive innovation toward these needs.

3. Legislation must be designed to provide incentives and support for such collaborations, while avoiding unwanted consequences.

Introduction

Good Morning. My name is Donald Lombardi and I am President and CEO of the Institute for Pediatric Innovation. We are a Cambridge, Massachusetts based nonprofit organization dedicated to increasing the quality of care of children by bringing more appropriate medical devices and drugs to the clinical treatment of pediatric patients.

Shortcomings of the technology transfer system

As others have testified, the medical device industry and the pharmaceutical industry have not invested effectively in commercializing devices and drugs that have been specifically designed for care of pediatric patients. I will address how the academic technology transfer system also fails to deliver the products needed for pediatric care.

I was the Chief Intellectual Property Officer of Children's Hospital Boston, responsible for managing that organization's compliance with the Bayh Dole Act of 1980. This law gives Federal grant recipients the right and mandate to transfer intellectual property arising from Federally sponsored research to for-profit companies. The intent is that companies will develop the products and make them commercially available, thereby benefiting the public. Companies licensed by Children's Hospital brought numerous products into clinical development and onto the market, resulting in tens of millions of dollars of revenue. However, very little of this commercial success resulted in new technology for the care to pediatric patients. My experience at Children's Hospital Boston is mirrored in the experience of technology transfer officers at all major pediatric institutions. Nearly all of the successful products arising from these institutions were focused on the clinical care of adults, because companies and investors who licensed the technologies were motivated to apply them for the largest and easiest-to-access adult markets.

Need for novel collaborations between public, private, nonprofit and for-profit organizations

We carried out an assessment of why even premiere pediatric institutions proved largely unable to cause products to be developed for treating children. We found that the traditional technology transfer

process focuses primarily on new basic biology discoveries made by research scientists. Most of this research lacks commercial proof-of-principle and requires significant investment even before testing in humans. Further, the program did not engage clinicians – i.e., doctors, nurses, and other patient care professionals – who know the most about the products needed for day-to-day care of patients. The scope of the problem demanded that it be approached on a national, multi-institutional basis. To address these issues, we created the Institute for Pediatric Innovation (IPI) as a nonprofit 501(c)3 organization. The IPI plan includes the following components:

1. IPI pediatric hospital consortium and need analysis. Before selecting products or technologies for development, we must understand the needs and priorities for pediatric and neonatal care. IPI has assembled a small consortium of leading pediatric care and research hospitals and is convening a board of pediatric experts to help assess the needs of the patients. The Hospitals are providing access to their clinicians and clinical operations to help identify those needs that can most impact quality of care, patient safety, and patient, parent and care-giver satisfaction. IPI will compare the information obtained from the clinicians with published market studies to fully understand the needs of the pediatric market.

2. Product selection criteria. IPI is comparing the information provided by the clinical thought leaders with needs and requirements for commercial feasibility in order to set priorities on areas for initial focus. Of the products with the greatest potential to save and improve lives, we will focus on those to which the members of the consortium can add most value in product design and clinical testing.

3. Product opportunity analyses. In its first year, IPI will select 5-7 products representing the greatest clinical need and greatest opportunity for near-term product realization:

- *Reformulated pharmaceuticals.* Existing pharmaceutical products that require different dosage or delivery forms for pediatric patient populations will be one focus. Today, physicians and nurses are forced to guess on dosage and use medication that has not been studied in the neonate or pediatric population. This opens the door for severe allergic reactions, overdosing or under dosing to treat severe infections, gastroenterology infections or urinary infections. In fact, new drug formulations often wait 2-3 years after the approval of a drug to even begin the dosing studies for pediatric and neonatal patients.

- *Re-engineered devices.* Today's physicians and nursing staff are forced to "jerry rig" products to save the lives of their small patients. Many medical products used in the adult population today, need be made not only smaller but also more flexible to avoid injury to a small body. Use of different materials, different anatomical curves and entry points and other factors need to be optimized for the pediatric patient. Alternative (FDA-approved) materials may provide better engineered products for neonate or pediatric care, optimizing the outcomes, and reducing hospital stays, potentially saving billions of dollars for the healthcare system. One day in the NICU for example, costs slightly over $40,000.
- *"Product imagination" brainstorming.* With market research and clinician input in hand, and with the support of a corporate partner interested in new products for neonatal care, IPI will conduct workshops with clinicians, design engineers, and market specialists to develop innovative product concepts for use in Neonatal Intensive Care Units. This initial project will serve as a basis for developing design practices that IPI will apply with corporate partners in other clinical areas such as pediatric orthopedics, cardiology, gastro-intestinal, neurosurgery and surgery.

4. Corporate collaboration. As a non-profit organization, IPI is only a part of the solution. In order to effect a major change in the current focus of device and pharmaceutical companies, IPI needs to collaborate with large corporations that will market the re-engineered or novel pediatric products to the hospital communities. Industry needs incentives to participate in improving pediatric care – such as grants, or additional federal tax exemptions – to offset the change their risk/reward calculus.

5. Access to government, foundation, philanthropic, investor, and corporate resources to finance product development. The consortium approach can reduce risk by identifying products that the pediatric market most needs. The IPI opportunity analyses will better qualify product opportunities. However, while many corporations are willing to contribute resources to the cause, they have not yet developed pediatric specific initiatives within their corporation, a critical goal of the success for IPI. As a nonprofit organization, IPI expects to be able to access philanthropic and government funds that do not require a return on investment to help finance the development phase of certain products.

Recommended guidelines for legislation

In seeking to help remedy the gap in availability of products optimized for pediatric care, Congress should:

- Create a reliable data source of clinical needs for which there is a demonstrable demand
- Provide the funding required to bring together clinicians, medical scientists, technologists, and businesses to direct innovation toward those needs
- Create incentives for industry and other stakeholders to collaborate in developing needed products
- Look for ways to expedite clinical testing and approval without risk to patient safety
- Avoid creating processes that add no value, create additional burdens or disincentives, or reduce the stakeholders' ability to meet clinical and scientific needs in pediatrics
- Assure that legislation meets the needs of all stakeholders including industry, FDA, and care-givers
- Remember that investments in improving children's health have the highest social return in quality adjusted life years

Mr. PALLONE. Thank you. I know it is an unusually large panel today. You can barely sit through it. But thank you for your testimony. I appreciate it. We are going to take some questions, and I will start with my own questions for 5 minutes.

I wanted to ask Dr. Crosse, you noted that drug manufacturers accepted 81 percent of FDA's written request to complete pediatric studies, and this is with regard to the on-patent drugs.

Ms. CROSSE. Yes.

Mr. PALLONE. And I am concerned about what happened to the other 19 percent of those. As I understand the process, they are referred to the Foundation for the National Institutes of Health for funding. Would you say that the process of sending them to FNIH is working or do you have any recommendations on how Congress might improve that part of the process?

Ms. CROSSE. It hasn't been working well because FNIH has not been able to raise sufficient private funds to cover the expenses of conducting these studies. In the first 4 years that this arrangement was underway, they were raising approximately $1 million a year. During the 1-year course of our conducting our work they raised no additional funds. They had raised a total of about $4 million which was insufficient to fund even one study. It only covered the cost of about half of the study expenses, and NIH stepped in with its own appropriations to pick up the remaining expenses for this drug because they felt it was so important to be studied.

We don't have specific recommendations for how this could be covered. The arrangement seemed a logical one at the time. It still called for private sector funding of the research, just as when the companies, the drug sponsors, paid for the studies but contributions have not been sufficient to FNIH to come anywhere close to filling the gap for these on-patent drugs when the drug sponsor declines.

Mr. PALLONE. OK. I am going to ask another money question, but I don't want everybody to answer this. But if someone wants to volunteer, we have been told by CBO that a continuation of the pediatric exclusivity program would score under the budget rules and as such a bill of this kind needs to have an offsetting tax increase or spending cut. Any of you want to recommend how to pay for the extension of the pediatric exclusivity program? You don't have to, but if anyone has an idea, I would like to hear it. Any volunteers here? Somebody is pondering. Dr. Lurie?

Mr. LURIE. Sure, don't reauthorize it in that sense. I mean, don't do it through patent extensions, do it instead through mandatory requirements as under PREA. That will save them money.

Mr. PALLONE. Well, that was easy, I guess. All right. Anyone else? Otherwise I will move on.

Ms. Belfiore, I really appreciate your being here today because your story about your family is truly compelling, and I wanted to thank you for sharing that for not only what you said and your family but for all the work that you do with the Elizabeth Glaser Pediatric AIDS Foundation. I am a parent. I have three children, and even as someone who is involved in developing these policies I don't think that it occurs to me to ask a physician when our children are sick as to whether or not the medicines they prescribe have been tested in children. In fact, almost three-quarters of the

drugs prescribed to kids have not been tested as you have said, and I think that is a startling statistic; and it is even more startling for children who suffer from life-threatening illnesses. Do you know how many drugs used for treating HIV/AIDS have currently been studied for pediatric use and just comment if you will on that because I am concerned in particular with the life-threatening illnesses and whether or not BPCA or PREA could have an impact.

Ms. BELFIORE. I do not know the number as to how many have been tested, but I do know that through BPCA that six new AIDS drugs have been approved for children. I was saddened and also happy to see that one of the drugs was the one that my daughter Mihaela formed a resistance to because she had not been given enough, saddened because she didn't get the use out of that drug. It is a very good drug in the adult population. People get a long time out of it, and my daughter did not get that time out of it.

But only because of this legislation is it now available for use in children. So I compliment what is being done here. It really makes a difference.

Mr. PALLONE. Thank you. I wanted to ask Mr. Rozynski. You speak of the lifting of the HDE which I guess is Humanitarian Device Exemption profit restriction in the Markey-Rogers legislation. Is this the most effective or is there any other incentives that you would suggest?

Mr. ROZYNSKI. Well, first, we appreciate the lifting of the restrictions so that way you in effect balance the incentives that you have in the adult population with those in the children's population. We don't have and we are not even seeking the concept of extended exclusivity for devices like you have for drugs. I am not sure that there is really an easy additional incentive that you could provide.

So therefore, I would say instead to just make sure the regulatory hurdles do not change in such a way that there is a disincentive to go into the market. Right now I think that there is balance in terms of how the FDA regulates this area. If the regulatory hurdles go too high, and as I say, we are not seeking any significant incentives, what you may end up doing is not reaching those twin goals of encouraging more devices, while at the same time having adequate information on these devices. Now, with regard to information, I would like to say that Stryker and other companies are prepared to give away in effect the knowledge that we have, the studies that we have, and to put them in a public database so that way if we can't figure out something in terms of ways to make this better or to address areas where perhaps we had some shortcomings, we are opening up this information to the public so that others can then perhaps use it to develop a better device. So we are prepared to open up as part of this legislation the studies that we do have and to share them in a public database as a way to stimulate more activity in the area of pediatric devices.

Mr. PALLONE. All right. Thank you. Thank you very much, all of you. Mr. Deal?

Mr. DEAL. Thank you. We have a variety of opinions here, some that say the present system is working OK, others who say it needs to be changed. But I think there is one thing that most everybody seems to agree with and that is the off-patent drugs is an area that we don't have any way to incentivize under the current system.

Dr. Crosse, do you have any suggestions as to how to deal with that particular issue? Obviously NIH is having difficulty coming up with the funding to do that.

Ms. CROSSE. No, sir, other than providing funds that are specifically available for undertaking these studies. I cannot see any way to incentivize the generic drug manufacturers to undertake the costs of conducting these studies.

Mr. DEAL. OK. We have a smaller market obviously for pediatric type applications of medicines. But I assume there are some drugs that are exclusively developed and marketed just for pediatric patients. Ms. Reilly, do you have any idea of how large that is compared with the overall approval of drugs?

Ms. REILLY. Well, what I can tell you is that there are about 200 medicines in development today specifically for pediatric populations. So while this pales in comparison to the overall number of drugs in development which is somewhere around 2,000 drugs in development, there is significant progress underway in our companies in terms of looking at research for pediatric populations.

Mr. DEAL. And I assume that there are some drugs that from the outset there is general acknowledgment that probably would never be appropriate for pediatric patients.

Ms. REILLY. That is true. I mean, obviously there are a number of drugs for which young children just don't happen to get those diseases. Osteoporosis is one example. But I think one thing that we have learned through the BPCA process is that for drugs, one drug for example, Tamoxifen, which is a drug to treat breast cancer was studied under the pediatric exclusivity program and was found to be effective for treatment of a rare disease affecting young girls. So I think even in the instances where we have drugs that one would assume are only for an adult population, oftentimes our companies have done research and found that that use is effective for different populations, in this case, a rare condition. And that was made available under BPCA.

Mr. DEAL. Mr. Lombardi, in your testimony I gathered that you were trying to figure out ways to develop this partnership between the industry and the pediatric hospitals which obviously are a very good incubator in which to either test devices or provide further research. You mentioned reformulation of drugs.

Mr. LOMBARDI. Yes.

Mr. DEAL. Now, I assume you were talking about off-patent drugs that are reformulated for more specific purposes. Would you elaborate on that and what obstacles do you encounter in that environment?

Mr. LOMBARDI. Thanks. Yes, we are focusing specifically, since we wish to get near-term products available to the clinicians, we are focusing specifically on off-patent drugs for which a better formulation or delivery method is needed. I will give an example. While still at Children's Hospital, we had a clinician who treated lead poisoning for 30 years with a product that had never been approved for children or for lead poisoning, but was long ago approved by the FDA in adults for a different use. It comes in a pill this size. It smelled of rotten eggs. It is a sulfur compound, and so we needed to find a company that would take this compound and reformulate it into something palatable, unsmelly, and digestible

for children. We made an arrangement, what I call a risk sharing arrangement in which they would risk and we would share to put the research into developing this formulation. They used formulation technology that has been used in many other drugs. So we had a compound that has a long experience in the clinic with adults and 30 years with children, and a formulation technology that has been previously used. So the question was how would we finance the clinical development of this, and we found an angel investor who studied this and realized that he could get the product through the clinical stage if things went well for between $1 million and $1.5 million. So he formed a small virtual company to take the product rights, and he has got his first investment now and the project will be developed in the clinic; and at the end of this process, he will sell this product off to a company that has got a sales force in pediatrics.

Mr. DEAL. Would that reformulated product be a patentable item in and of itself?

Mr. LOMBARDI. Well, the composition is not patentable, but the formulation is patentable. It is not a strong patent because people can come up with an alternative formulation that may accomplish similar results. But it will give this party a degree of exclusivity.

Mr. DEAL. Is there anything we can do in that arena that would incentivize these reformulations? Is there anything there you see either through the patent process or through some degree of exclusivity or something because it appears to me that more than likely that is where the off-patent is going to produce results is in reformulation of some type.

Mr. LOMBARDI. I don't have a specific proposal, but I think if there is a way of broadening the concept of the orphan exclusivity to cover pediatrics for pediatric-specific formulations, that would be helpful. Second, another area that we worked on was with a different formulation company on a different product, and that company applied for, and I understand recently was awarded, an SBIR grant from the NIH for the development and clinical testing of that product. So funding always helps because if the product development phase can be accomplished on monies that do not require a return on investment, then the calculus for having the product be able to sustain itself in the market changes significantly. Thank you.

Mr. DEAL. Thank you.

Mr. PALLONE. Dr. Burgess.

Mr. BURGESS. Thank you, Mr. Lombardi. Mr. Rozynski, it seems I guess fortuitous that you are sitting there together at the end of the table because Mr. Rozynski, you talked about having the ability for having someone to be a matchmaker between inventors and manufacturers, and Mr. Lombardi, you are talking about stimulating research and development; and I hope you two will at least exchange business cards before the hearing is over because that does seem like an enormously worthwhile activity. But Mr. Rozynski, I wonder if you could tell us, from your perspective, are there concerns about the legislation we are working on or are there things that we can do that will be injurious to going forward with new devices and new procedures, and what concerns would those be?

Mr. ROZYNSKI. Thank you for the question. It is a very interesting question which we have thought about quite a bit. I would first like to say that we support the legislation. We are here to support it, and we want to see its passage. We believe that this is an important step forward. So we are not really looking to nitpick. But I think about how devices are developed in the small populations, I mean, we even have situations where we work with one doctor on one child to develop one custom device. And so when you look at some of the additional regulatory issues that are raised within the bill which would require multi-year long studies, we agree with a lot of that, but at the same time, we are trying to scratch our heads and say what will this do to people who today serve that market and want to continue to serve that market, that individual patient, that doctor, that small population. Is there is a potential regulatory hammer hanging over their head that they may end up having all sorts of additional costs and additional studies that they are going to have to do? So we are not against it, we are just saying this is really a difficult question. But in the end, we want to make sure that the net effect of the legislation is to get more devices to market and to get more information developed. And as I said, we are prepared with other companies to open up all of our studies to share the information to do the match-making. But we want to make sure when we change FDA's current authority, we do not create such an imbalance that people are further encouraged to go serve those adult populations as opposed to serving those much smaller children's populations where the incentives in the end really in the area of medical devices are not highly financial. You are not going to make a lot of money doing these custom devices, doing these small developments. So that is really the challenge, tomake sure we address those questions and we get the balance right.

Mr. BURGESS. And yet, I mean again, your compelling testimony about the treatment of childhood sarcomas, I mean I can remember a University of Texas football player at age 18 played a football game, had a pathologic fracture, and 2 weeks later his leg was amputated to save his life. I mean, you have now changed that equation forever for the better. And I for one am grateful that those things are available as there may indeed have been one doctor and one manufacturer working together to try to come up with, hey, can we do something better for this patient and now we can extrapolate it to still a small but a much wider population. So I guess if we can build in the flexibility for the most unique situations into the legislation, that is certainly something that I am interested in trying to do.

Dr. Gorman, I think you and Dr. Crosse both discussed how because of the lack of the data and the research on pediatric indications, a lot of the things that you did during your practice life are essentially off-label uses of medication; and I was an OB/GYN by trade before I came to Congress, so I can promise you, I can think of one or two compounds that actually stayed approved for use during pregnancy. No one wants that liability. We saw what happened to Bendictin 30 years ago, and no one is going to take that chance unless it is something exclusive to pregnancy like treating premature labor. And yet, we hear testimony from Dr. Zerhouni and

others at NIH that we are embarking on an age of personalized medicine. How do you see these studies on the pediatric side working in that environment? Will we just develop systems where because we are working on personalized medicine, just by its nature we take into account the pediatric population and the obstetric population, the prenatal population as well as the adult population?

Mr. GORMAN. Pediatricians, maybe more than any other group, are awaiting the world of personalized medicine where we can treat the person with the disease, rather than the disease and the person. We have laid the ethical and legislative structure for the eventual advancement into all the populations that you talked about. Today, NIH is studying vaccines in mothers to protect children. So hopefully in your future or your children's future as a practicing OB/GYN, there will be more and more medications——

Mr. BURGESS. No, they are not going to do that. My liability will fix that for us.

Mr. GORMAN. Well, whatever career path they take, they will have the ability to have drugs that are studied in their population and personalized medicines that are studied in their populations. But the framework that these particular pieces of legislation have formulated, with all of their small warts but major successes at the same time allows other groups of specialized populations to see the path to their own successful futures.

Mr. PALLONE. I am sorry. We started voting, and there is only about 8 minutes left.

Mr. BURGESS. I beg your pardon.

Mr. PALLONE. So I am going to just ask Markey to ask a few questions, and then we are going to go over and finish up. Thanks.

Mr. MARKEY. I thank you, Mr. Chairman, and by the way, I thank you for your leadership on this issue and the focused way in which you are bringing all of these issues to the attention of the Congress and I thank Chairman Dingell as well for his comments yesterday on Avandia and the need for FDA reform. I agree with him 100 percent that this is one more example why we need legislation to reform the drug safety system at the FDA, and I was extremely pleased that Chairman Dingell said that he plans to address FDA's shortcomings and safety while writing legislation to reauthorize PDUFA. I think that is the right context for us to do it.

I have just two quick questions. Dr. Gorman, what has happened since 2004 to convince the American Academy of Pediatrics that it is important to act now to get the legislative changes that is in the Markey-Rogers bill?

Mr. GORMAN. One of the wonderful things about being a pediatrician in practice is that you get to see what works and doesn't work and then get to modify what doesn't work, hopefully with things that are more effective. For 10 years we have watched FDAMA and BPCA, but now for 5 years we have watched PREA work; and we have seen some things that it does very well, and we have seen some things that it doesn't do as well as we would like. Some of the BPCA and PREA use slightly different standards and slightly different formulations of thought on how they approach pediatric labeling. And we think they should be unified. We think that the results that are generated from studies, both the positive and the

negative, should be reflected on the labels that the American consumer uses when deciding and their practitioners on the safety of the drugs.

Mr. MARKEY. And why is expanded post-market monitoring authority important?

Mr. GORMAN. We think that expanded post-marketing authority is important for at least three separate reasons. One is that we think that you get more safety data when a drug is being used by 2 million people than when it is being used by 300 people in a clinical trial. So the majority of data is presented after a drug is approved. So the safety data is there for being mined.

Mr. MARKEY. OK.

Mr. GORMAN. Second, there is the possibility that pharmaceutical companies promise post-marketing studies that then don't get done. And the track record for those being done is outlined in the GAO report about how many were promised and how many were performed. And third, we think that pediatric patients, because they are a clean system, in other words, generally they have very few other diseases, that they are a system in which you can see safety signals more clearly.

Mr. MARKEY. OK. So, Mr. Rozynski, could you tell me why you now believe that this Markey-Rogers Pediatric Devices bill should pass as well?

Mr. ROZYNSKI. We are a very early and a very big supporter of this bill. We think this bill is a step forward to focus attention on the need for more pediatric devices. We do believe that there are really twin goals here, of course, which are encouraging more pediatric devices and also encouraging the development and sharing of pediatric device information. We want to make sure that both of those goals work together. I know there have been a few questions raised about when and where do you collect this additional information. We want to provide more information. We also want to make sure that we do not request information in a way that we continue to have companies migrate towards developing devices for the adult population at the expense of the pediatric population. We think this bill is a big step in that direction and at the same time, we want to make sure that in the end, those twin goals are achieved, which is more devices.

Mr. MARKEY. I thank you and I also want to clarify that the post-marketing provisions in our legislation will give the FDA more authority to require monitoring of pediatric devices at the Secretary's discretion. It does not require clinical trials in the post-market setting. This was a recommendation of the Institute of Medicine, and we don't have much time left on the roll call.

Mr. Chairman, again, I thank you for your leadership. I thank Mr. Dingell for his comment, and I thank you for your indulgence.

Mr. PALLONE. Thank you, Mr. Markey, and thank you all. We only have 3 minutes left, but I really do want to thank you all for spending the time. As I always say, within the next 10 days, you may get additional questions from some of us that we would ask you to respond to in writing; and obviously, we are going to use your testimony as we move forward with reauthorizing some of these initiatives. So thank you again, and this hearing is now adjourned.

[Whereupon, at 1:15 p.m., the subcommittee was adjourned.]

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