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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

[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

[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

[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.

Attachment 1

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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.