American Academy of Pediatrics

TESTIMONY OF
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on behalf of the
AMERICAN ACADEMY OF PEDIATRICS

before the

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

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Mr. Chairman, members of the committee, I am Richard Gorman, MD, FAAP, a practicing pediatrician who has taken care of infants, children and adolescents for over 29 years. I am here today representing the American Academy of Pediatrics (AAP) in my official capacity as chair of the AAP Section on Clinical Pharmacology and Therapeutics. It is through my practice, Pediatric Partners in Ellicott City, Maryland where I see 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.

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.

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

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

BPCA and PREA work together as an effective two-pronged approach to generate pediatric studies. PREA provides FDA the authority to require pediatric studies of drugs when their use for children would be the same as in adults. BPCA provides a voluntary incentive to drug manufacturers of an additional 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 119 drugs.[1] By comparison, in the seven years prior to FDAMA, only 11 studies of marketed drugs were completed, though 70 studies were promised. Similar data tracking PREA's effectiveness is not publicly available. AAP hopes this year's reauthorization will create that tracking system.

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

For example, pediatric studies and resultant labeling have:

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

- 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.

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

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

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

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

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

BPCA AND PREA ARE STILL ESSENTIAL TOOLS

Despite the advances resulting from BPCA and PREA, there remains much progress to be made. Children remain second-class citizens when it comes to drug safety and efficacy information. Currently, nearly two-thirds of drugs used in children are still not labeled for children.[2] Almost 80% of hospitalized children receive at least 1 one drug prescribed to them for an off-label use.[3] For children, off-label use is the rule, not the exception, because of the scarcity of prescribing information for this population. Therefore, both BPCA and PREA are still crucially important and must be reauthorized this year, including needed improvements.

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

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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

Increase the dissemination, transparency, and tracking of pediatric drug information. Dissemination of pediatric information to families and healthcare providers should be increased in both BPCA and PREA. If families choose to involve their children in a clinical trial for a drug, then the drug label should reflect that study. The Government Accountability Office (GAO) found that about 87% 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 the written request process used by FDA can be improved. Increased transparency will be beneficial to pediatricians, sponsors and families. AAP recommends that written requests be made public at the time FDA awards exclusivity and that each written request be allowed to include both off-label and on-label uses. Moreover, because we recognize that FDA has improved the pediatric study written requests since 1997, we recommend that the Institute of Medicine be engaged to review a representative sample of all written requests and pediatric assessments under PREA. This scientific review will provide recommendations to FDA to continue to improve the consistency and uniformity of pediatric studies across all review divisions within the FDA's Center for Drug Evaluation and Research.

Information regarding the number of written requests issued as well as information regarding pediatric studies and label changes made as a result of BPCA is tracked and posted at FDA's 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 review and tracking of all pediatric studies requested or required by FDA, including the ability to require labeling changes.

Expand study of off-patent drugs. BPCA and PREA work well for new drugs and other on-patent drugs for which increased market exclusivity provides an appropriate incentive. However, for generic or off-patent drugs, BPCA and PREA have had a less effective reach. At the last BPCA reauthorization, Congress tasked the National Institute for Child Health and Human Development (NICHD) with creating a list of off-patent

[4] GAO 2007; 16

drugs needing further study in children and with conducting those needed studies. Although Congress never appropriated any funding to NICHD for this purpose, NICHD nevertheless has made significant progress identifying important off-patent drugs in need of study and starting clinical trials to study these drugs. AAP recommends that the role of NICHD be expanded in the current reauthorization to include study of the gaps in pediatric therapeutics in addition to generic or off-patent drugs. We also recommend PREA be strengthened so that needed pediatric studies can be conducted while drugs remain on patent.

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

Maintain quality and number of pediatric studies while addressing "windfalls."
Providing drug companies 6 months of additional marketing exclusivity has been enormously successful in creating pediatric studies. The studies and label changes highlighted earlier in my testimony demonstrate this. Recent data shows that for the large majority of drugs, the return to companies for responding to a written request has not been excessive. The Journal of the American Medical Association published a study in February that showed the return to companies for performing pediatric studies varies widely.[5] Most companies who utilize BPCA made only a modest return on their investment in children.[6] However, for 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. The Academy has pledged to review any proposal for limiting the exclusivity awarded under BPCA using two criteria: first, any change must not reduce the number of drugs studied in children. GAO found that 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

[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

written request from FDA would undermine the essential goal of BPCA. We now have data to show that simply cutting the incentive from 6 months to some lesser number across-the-board will certainly reduce pediatric studies and we cannot support such proposals.

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

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

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

CONCLUSION

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

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

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