American Academy of Pediatrics

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Testimony of
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On behalf of the
American Academy of Pediatrics

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Health Subcommittee

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Mr. Chairman, members of the subcommittee, I am Daniel Frattarelli MD FAAP, a practicing pediatrician and Chair of Pediatrics at Oakwood Hospital and Medical Center in Dearborn, MI. I am here today representing the American Academy of Pediatrics (AAP) in my official capacity as chair of the AAP Committee on Drugs. The AAP is a non-profit professional organization of 62,000 primary care pediatricians, pediatric medical subspecialists, and pediatric surgical specialists dedicated to the health, safety, and well-being of infants, children, adolescents, and young adults. As a pediatrician, I see first-hand the need for all children to have medicines that are studied for their use and are in dosage forms that are made for their size and stages of development.

The testimony I give today is supported and endorsed by the Elizabeth Glaser Pediatric AIDS Foundation. More than two decades ago, Elizabeth Glaser began lobbying the halls of Congress to call for more research for drugs to treat HIV/AIDS in children. The Elizabeth Glaser Pediatric AIDS Foundation carries on her work today, advocating for children in the U.S. and around the world to have access to the best prevention and care that science and medicine have to offer.

THE ACCOMPLISHMENTS OF BPCA AND PREA

I am here today on behalf of the AAP 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 thank this subcommittee and full committee for its strong support of these programs throughout the years. I begin my testimony today by saying enthusiastically and without reservation that through BPCA and PREA we have gained more useful information on drugs and biologics used in children than we had in the seventy years prior to their enactment.

I wish to extend the Academy's sincerest thanks to Representative Anna Eshoo for her long-standing support and for championing these important laws for children. Although not the subject of today's hearing the Academy also wishes to acknowledge and thank Representatives Mike Rogers and Ed Markey who authored the Pediatric Medical Device Safety and Improvement Act of 2007. The Academy sees these three laws as a complementary package of vital pediatric drug and device laws and all three should be reauthorized together this year. We also recognize Senators Jack Reed and Patty Murray for their outstanding leadership in championing these laws in the Senate.

BPCA and PREA 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 little. It is vitally important for these pediatric subpopulations that these laws be reauthorized.

In a 1977 landmark statement, the AAP's Committee on Drugs, which I now have the privilege of chairing, said that it is unethical to adhere to a system which forces physicians to use therapeutic agents in an uncontrolled experimental situation virtually every time they prescribe for children. The Committee also said that it is not only ethical, but also imperative that new drugs to be used in children be studied in children under controlled circumstances so the benefits of therapeutic advances will become available to all who need them.

In the time since that statement was published, we have gone from a situation where about eighty percent of time, the drugs we were using in children did not have FDA-approved pediatric labeling to today where that number is down to about fifty percent. That success is a direct result of BPCA and PREA. However, because half of drugs used in children still lack pediatric labeling, off-label use remains an unfortunate but necessary practice. As Congress considers legislation related to prescription drugs, such as drug shortages, the Academy asks policymakers to ensure that off-label uses of therapeutic agents be part of the discussion since it is the standard of care for our patient population.

BPCA and PREA work together as an effective two-pronged approach to generate pediatric studies. 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. PREA provides FDA the authority to require pediatric studies of drugs when their use in children is for the same indication as for adults.

BPCA was first enacted in 1997 and later reauthorized by Congress in 2002. PREA was passed in 2003 and reauthorized together with BPCA for the first time in 2007, creating a unified approach to pediatric drug testing and labeling at the FDA. In 2010, Congress extended BPCA to biologics for the first time. Since 1997, 426 drug labels have been updated with pediatric information including 147 under BPCA, 181 under PREA, 50 under both BPCA and PREA, and 48 under the precursor to PREA, the Pediatric Rule.

As a clinician, I cannot overstate the importance of what we've learned through the pediatric studies generated by these laws. Pediatric studies conducted under BPCA and PREA challenged what was previously thought about therapeutics in children. In many cases, studies and resultant labeling altered the dosages we give our patients. In others, drugs previously thought to be safe and effective in children proved not to be. And, pediatric studies have led to more effective formulations that are more palatable for children. To put it simply, the more we learn, the more we realize what we didn't know.

CHANGES TO BPCA AND PREA IN 2007 MAKING AN IMPORTANT IMPACT

In 2007, BPCA and PREA were reauthorized for the first time together. Congress took advantage of that historic opportunity and created the most integrated, well-coordinated system at FDA to pursue pediatric safety and efficacy labeling that we have seen to date.

In 2007, the AAP argued 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. Prior to 2007, there were studies in which families chose to enroll their children for which resultant data does not appear in a products label. I am proud to report that based on data from the Government Accountability Office (GAO), all pediatric studies completed under BPCA and PREA from 2007 until 2010 resulted in labeling changes that included important pediatric information.

Since the 2007 reauthorization, the number of drugs and biologics studied in children rose dramatically: 130 products between 2007 and 2010, compared with 250 products between 1997 and 2007. The incentive under BPCA is well-targeted and is increasingly more popular over time. According to GAO, the number of declined pediatric studies under BPCA fell from 19% between 2002 and 2005 to 5% between 2007 and 2010. Drugs and biological products studied under BPCA and PREA represent a wide range of diseases in children, including those that are common or life-threatening such as cancer, HIV/AIDS, diabetes, allergy and asthma.

The 2007 reauthorization of PREA established the Pediatric Review Committee (PeRC), an internal FDA committee that is providing assistance in the review of pediatric study results and increasing the consistency and quality of such reviews across the agency. The PeRC has played a vital role in helping to better integrate BPCA and PREA and pediatrics generally within FDA and should continue to be supported and strengthened.

BUILDING ON WHAT WE'VE LEARNED FOR FUTURE IMPROVEMENTS

With each reauthorization of BPCA and PREA, we have learned how truly essential it is for children that these laws exist and evolve. Congress has made changes to these programs that have monumentally improved how they function. Based on what we've learned about these laws since 1997, the Academy offers several recommendations for improvements to BPCA and PREA in 2012.

Remove barriers to earlier pediatric studies

PREA is a premarket requirement for safety and effectiveness. However, the law does not require the submission of a plan for pediatric studies until the time a company submits its application or supplement, which is at the end of the adult drug development process. The precursor to PREA, the Pediatric Rule, required that drug companies discuss and plan for pediatric studies no later than the end of phase 2. The laws of the European Union require the submission of a pediatric investigational plan at end of phase 1. It is important to remember that under PREA, failure to submit a pediatric plan at the time of the submission of a drug application cannot delay the approval of the drug in adults.

Submission of a pediatric plan so late in the process can lead to insufficient and inappropriate study plans and delays of important pediatric data. Pediatricians and families will get better quality pediatric data if discussions with FDA's PeRC happen earlier in the drug development process. And, by giving companies more time to work with FDA on a realistic pediatric plan, we will reduce the need to rely on deferrals, too many of which are well past their agreed-upon due date.

In the PREA retrospective review required by Congress in the 2007 reauthorization, FDA found that with 17 review divisions within the Center for Drug Evaluation and Research (CDER) and few or no pediatricians in some divisions, "approaches in the implementation of PREA, including the level of detail in reviewing pediatric protocol plans, were quite variable." FDA said that many of the pediatric postmarketing requirements listed in the approval letters were described in general terms in "one to three sentences".

FDA found that in cases where PREA studies did not demonstrate efficacy, it is possible that the process could have benefitted from a more detailed pediatric plan being submitted by the applicant before approval. FDA went on to say, "where there was evidence of specific discussion and documentation of the studies needed to fulfill PREA requirements before commencement and/or submission of the studies, the PREA assessments generally were of higher quality."

AAP recommends amending PREA to require the submission of a proposed pediatric study plan at the end of phase 2 that includes a description of the study objectives, age groups, study design, relevant endpoints, statistical approach, and timeline for expected completion of the study. Within a reasonable timeframe, the PeRC should approve or reject the proposed pediatric study plan.

Improve accountability

Based on the data available today from FDA, within CDER, 78% of PREA studies that were due after September 27, 2007 are still pending today or were completed after their agreed-upon due date. Within CBER, 54% of PREA studies that were due after September 27, 2007 are still pending today or were completed after their agreed-upon due date, including several childhood and flu vaccines. These numbers only include studies that were deferred after September 27, 2007 and do not include studies that were deferred prior to 2007.
Under current law, FDA is prohibited from delaying the approval of a drug or biologic in adults even if the applicant or sponsor has failed to comply with its PREA requirement. AAP supports the principle that adults should not be denied access to effective therapies while studies in children are underway. However, it cannot be the case that delays in studies become permanent once a drug is approved for marketing. Once a product is approved, FDA treats PREA requirements as post-marketing requirements. PREA prohibits FDA from using any existing enforcement mechanisms under section 303 of Federal Food, Drug and Cosmetic Act even though those enforcement mechanisms explicitly pertain to post-marketing requirements that involve adult populations. While we hope enforcement action would never have to be taken, FDA should have enforcement tools for children comparable to those for post-market requirements in adults to ensure that pediatric data is gathered as soon as possible. Congress may also want to consider whether the benefits of BPCA's market exclusivity remain available for companies who are ignore their PREA requirements or have not worked with FDA to establish a new completion date and other necessary amendments for their studies.

There are reasons why pediatric studies might take longer than anticipated. For instance, companies may encounter problems with patient enrollment. However, FDA currently does not distinguish between delays that are for good, justifiable cause and those that are not. The AAP recommends giving FDA the authority to grant deferral extensions when there is good cause.

Promote studies in younger age groups

Premature babies and babies born with congenital or genetic conditions routinely require numerous drugs and other medical interventions to survive their first days, weeks and months. AAP's neonatologists report that almost 90% of the agents that are routinely administered to neonates (babies from birth to age 1 month) have never been adequately studied for safety, dosing, or efficacy in this unique population. As such, these tiny children, remain second-class citizens when it comes to drug safety and efficacy information. While neonatal drug research faces many barriers that are scientific and ethical, GAO and other experts have identified that greater neonatology expertise at the FDA would aid drug development for this population. AAP recommends that a dedicated neonatologist be added to FDA's Office of Pediatric Therapeutics. AAP also believes that FDA should be required to ensure that BPCA written requests include

neonates wherever possible and if they are not included, the written request should include a statement describing the rationale why. Lastly, PREA requirements are triggered when an applicant submits an application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. We believe new age group should be added to this list so that pediatricians would have data for as young an age group as the FDA determines necessary.

Increase transparency

As we learned in the 2007 amendments, increased transparency benefits policymakers, families, researchers and other stakeholders. Currently, pediatric researchers cannot access information on what drugs are currently being studied under BPCA and cannot access written requests and the corresponding medical, statistical, and clinical pharmacology reviews for drug studies completed under BPCA prior to 2007. In some cases prior to 2007 where a company was awarded 6 months of exclusivity for conducting pediatric studies, the labeling does not reflect the results of those studies. The reviews of those studies should be made available to the public just like they have been for studies conducted after 2007.

AAP also recommends that BPCA written requests be made public at the time they are accepted or declined rather than at the time exclusivity is granted. At present, BPCA study requests that are declined by drug companies are never made public. Declined BPCA study requests represent an important gap in pediatric data and companies should have the opportunity to state their reasons for declining the study request.

Make PREA permanent

The AAP commends the House of Representatives for making PREA permanent as part of the FDA reform bill it passed in 2007 and we call upon Congress to make PREA permanent in 2012. The FDA currently has the permanent authority to ensure the safety of drugs used in adults. Children deserve the same. Congress need not debate every few years whether we should continue to require safety and efficacy information on drugs used in children. It is useful, however, to reevaluate the exclusivity program periodically to ensure that the incentive offered achieves its desired goal despite changes in the dynamic pharmaceuticals market. Congress should have the opportunity through a 5-year sunset 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 drugs.

Continue promising pediatric study program at NICHD

BPCA and PREA work well for new drugs and other on-patent drugs for which additional market exclusivity provides an incentive. However, some of the most commonly-used drugs in children are off-patent and beyond the traditional reach of these programs. To address this need, BPCA tasked the National Institute for Child Health and Human Development (NICHD) and the National Institutes of Health (NIH) with creating a priority list of pediatric therapeutic needs in off-patent products and conducting those needed studies. NICHD's program has grown into a promising effort to increase pediatric labeling, with more than a dozen clinical trials completed or ongoing and dozens more awaiting funding to initiate the trials. AAP recommends that NICHD's program continue and be reauthorized without changes at its fiscal year 2008 authorized level of $200 million.

By contrast, the Foundation for the National Institutes of Health (FNIH) which is given authority to collect donations from pharmaceutical companies to fund declined BPCA studies has collected no such donations to enable it to complete any BPCA studies in the history of its involvement with BPCA studies. Therefore, its mandate to conduct pediatric studies of on-patent drugs only serves as a barrier to NICHD conducting those studies and, as such, should be eliminated. However, the Academy recommends retaining the legal authority of FNIH to maintain an emphasis on children and raise money for important pediatric needs, such as training pediatric clinical investigators, building pediatric research networks, and studying pediatric disease mechanisms.

CHILDHOOD CANCER AND OTHER RARE DISEASES

Experts in pediatric oncology have suggested that PREA would better serve the needs of children with cancer if it was allowed to require the study of a drug in children even if it is intended to treat a cancer—like lung cancer—that does not occur in children. The AAP believes this idea has merit and deserves serious consideration by Congress.

The AAP also underscores the importance of the Orphan Drug Act in stimulating drug development for populations with rare diseases, half of which are children. Families with children facing these devastating diseases require the special consideration the Orphan Drug Act, BPCA and PREA provide.

CONCLUSION

I would like to thank the subcommittee 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. For the health and well-being of all children, we urge their renewal, as well as the renewal of the Pediatric Medical Device Safety and Improvement Act, as part of the package of FDA bills under consideration by the subcommittee.

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