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"Ensuring Safe Medicines & Medical Devices for Children"

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

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

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

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

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

BPCA and PREA: Catalysts for Unparalleled Advancements in Pediatric Drug Research, Safety & Effectiveness

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

PREA gives the FDA the authority to require a pharmaceutical manufacturer to conduct pediatric studies for certain uses under clinical development. BPCA goes beyond PREA, encouraging manufacturers to ask, "Where are the unmet needs for children?"—including

off-label uses—and then to pursue meaningful answers to that question under the guidance and direction of the FDA.

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

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

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

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

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

This is, of course, no criticism of Dr. Nelson. He made his best judgments—as did we all—in the face of very limited information. But when the health and well-being of children are at stake, we know that best judgments absent clinical data just aren't good enough. Children—and all patients—deserve better.

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

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

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

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

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

Johnson & Johnson echoes this sentiment. The area of pediatric drug development, as I've witnessed it, has burgeoned only in the last 10 years. There remains great need and

potential for further discovery. To sustain the level of momentum that BPCA and PREA have spurred, and to strengthen the framework for further pediatric drug studies and infrastructure, we strongly believe that the sunset clauses in both pieces of legislation should be removed swiftly and permanently.

Removing the Sunset Clauses in BPCA and PREA: Sound Policy for Ensuring Further Advancements in Pediatric Drug Research

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

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

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

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

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

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

Conclusion

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

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

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