National Perinatal Association

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The Development of New Pharmacological Therapies for Infants

The National Perinatal Association's Position of Support for

Senate Bill S.2041 - Promoting Life-Saving New Therapies for Neonates Act of 2016

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INTRODUCTION

Historically children, newborn infants in particular, have been underrepresented in the development of pharmaceuticals and biologics with pediatric indications, appropriate dosing, and risk benefit profiles. A new law has been proposed to address this disparity and further encourage new pharmaceutical development for newborns: United States Senate Bill S.2041 - Promoting Life-Saving New Therapies for Neonates Act of 2015.

Despite Congress recognizing that children's interests are not being met with pediatric pharmaceutical development, not much progress has been made to meet this need. As a result, efforts to offer even more incentives to pharmaceutical companies such as those described in Bill S.2041 are being made. After a careful review of the history of pediatric pharmaceutical development, the National Perinatal Association supports this bill. At the same time, we call for accountability, transparency and a true public-private collaborative effort in the process of pharmaceutical development, testing, marketing and pricing of new products.

BACKGROUND

Development and approval for new pharmaceuticals for neonates (newborn infants up to 28 days of age) is insufficient to meet the needs of our most fragile patients. Surfactant had its origins in the academic research labs and was subsequently later transitioned to a commercial pharmaceutical product. Many of the pharmaceuticals utilized in Neonatal Intensive Care Units (NICUs) have their indication and dosing extrapolated from adult indications and dosing. This type of "off label" usage is necessary because for so many drugs, there are no Food and Drug Administration (FDA) approved use or dosing for neonatal-specific indications. These pharmaceuticals may actually provide clinical benefit as determined either anecdotally by clinicians or through small-scale clinical trials; their lack of FDA approval in some cases may be more representative of the fact that an adequate amount of research to ensure both safety and efficacy has never been done in babies. Occasionally, pharmaceuticals that are used "off label" in neonates have previously unrecognized serious and sometimes life-threatening adverse effects, such as Sildenafil, which then mandates the addition of specific warnings limiting their use. Although an FDA indication specific to the neonatal population does not guarantee an absence of serious adverse effects with widespread use of a new pharmaceutical or biologic, appropriate FDA oversight can provide assurances that a pharmaceutical or biologic has undergone rigorous and extensive testing of safety and efficacy in this population.

Neonates have their own unique pathology and physiology that makes them distinct from older children and adults. They have a range of age-specific medical issues, including metabolic and organ systems that are still maturing, less reliable metabolism and decreased clearance of pharmaceuticals and biologics. This is particularly true in preterm infants (those born at less than 37 weeks completed gestation). Because results of studies in older children and/or adults cannot be easily extrapolated to this distinct and vulnerable population, we need research and development of pharmaceuticals intended specifically for them.

There are many barriers to development of new pharmaceuticals or biologics for neonates. First, because neonates represent a relatively small target patient population, it takes longer for a company to recoup the significant investment it takes to develop, test and market a new pharmaceutical or biologic. Pharmaceuticals and biologics for neonates may qualify for "orphan" status, meaning that they treat fewer than 200,000 people in the U.S. on an annual basis or sales are not expected to recover the costs required for their development and marketing. This is particularly relevant since only about 200,000 preterm newborns are admitted to NICUs each year, and not every preterm infant will develop all of the conditions for which medications to improved prevention and/or treatment are needed (for example, retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia).

Second, performing clinical trials to determine pharmaceutical safety and efficacy in neonates is fraught with challenges. One issue is the enormous degree of variability in the population of preterm infants. Metabolic systems and processes (absorption, distribution, metabolism and excretion) can differ markedly from an infant that is born at 22 weeks gestational age, the cusp of viability, to infants born at 36 weeks and beyond. A pharmaceutical or biologic that might be safe and well-tolerated by a 36-week gestation infant might be toxic to one born at 22 weeks. Consequently, trials need to be done in large numbers of preterm infants with a wide range of gestational ages. To realistically accomplish this goal, multicenter trials are essential. Coordinating such a research endeavor is complex and costly.

Third, conducting research on medication safety and efficacy in neonates involves the ethical consideration of obtaining informed consent from parents who are already distressed about having a sick baby. Even if basic science and laboratory research or research in populations of older children or even adults has been conducted to suggest a particular pharmaceutical or biologic may be helpful in the preterm infants, there is no way to accurately predict all potential side effects and adverse events so as to inform parents.

Finally, pharmaceutical development is an increasingly expensive proposition. The Tufts Center for the Study of Drug Development's 2014 has estimated that the cost to develop and bring a pharmaceutical to market is now $2.6 billion. Although this estimate has been challenged, there is no doubt the cost is astronomically high. (1) While innovations may come from university scientists through basic science or "bench" research around certain pharmaceuticals or biologics that could ultimately be useful in helping to prevent or treat conditions that are seen in neonates, the universities themselves are ill-equipped to take the risks and absorb the costs of conducting research on the scale and scope that is necessary to gain FDA approval of new medications, especially when approval is by no means assured. Similarly, universities are not in the business of producing, distributing, and/or marketing new pharmaceuticals or biologics; these tasks all are dependent on private industry.

In the last several decades, FDA has focused increased attention on the unique medication development and utilization needs of pediatric patients. In 1979, the FDA first required pediatric information to be included on pharmaceutical labels. In 1994, pediatric indication for pharmaceuticals was granted if pediatric dosing was established. It was not until 1997, when the Food and Drug Administration Modernization Act (FDAMA) was passed, that incentives were created to encourage drug testing of already branded drugs in pediatric patients; the main incentive was a 6-month patent extension and hence market exclusivity (including adult use of the medications) for any pharmaceuticals developed as a result of this legislation, termed "pediatric exclusivity." At

the same time, pharmaceutical manufacturers were required to provide pediatric testing data with all new pharmaceutical applications.
The following year, legislation passed to require pediatric testing as part of any new pharmaceuticals, which had potential uses in pediatric patients; this was known as the Pediatric Final Rule. Four years later, a federal court overturned this rule, but in 2003, Congress reinstated it through the Pediatric Research Equity Act (PREA). In 2002, the Best Pharmaceutical for Children Act (BPCA) was passed, extending the previously granted 6-month exclusivity extension provision through the year 2007. This law also allowed the FDA to invite the National Institute of Health (NIH) to obtain pediatric data on pharmaceuticals for which manufacturers declined to obtain the data; pediatric study results could then lead to approval of the pharmaceuticals for pediatric indications. One situation in which pharmaceutical manufacturers frequently declined to gather data on pediatric patients is in the case of generic pharmaceuticals, because these don't have the potential for large financial returns, such as might be seen with newer patented pharmaceuticals. Further, generic products are not eligible for the Orphan Drug Act.

These laws have cumulatively had the positive effect of stimulating a large number of clinical pharmaceutical trials in children, resulting in over 500 product labeling changes. In some cases, FDA-approved indications for use in children were added to pharmaceuticals already on the market; in other cases, new warnings and/or new dosing instructions were added to pharmaceuticals previously approved only for adults; and in still others, the clinical trials failed to show efficacy in infants and children. But while the number of studies leading to increased numbers of medications with pediatric labeling has expanded significantly over the past 10 years, there continues to be a dearth of new pharmaceutics and biologics developed specifically for the neonatal population.

NPA POSITION OF SUPPORT

While the National Perinatal Association would prefer that government-sponsored financial incentives were not necessary to encourage pharmaceutical companies to pursue pharmaceutical development for neonates, it recognizes that relying solely on government intervention and/or mandates for companies to develop and produce such pharmaceuticals is neither a practical nor a desirable solution in our society. The intent of Bill S.2041 - Promoting Life-Saving New Therapies for Neonates Act of 2015, is to address this situation by providing greater financial incentives to spur innovation. This bill would create a transferable "Neonatal Drug Exclusivity Voucher." Companies that test and develop pharmaceuticals and biologics for preterm or full-term newborns that are on a Priority List of Critical Needs for Neonates (also created by the bill), would be eligible to receive the voucher. The voucher would enable the product sponsor to extend their exclusivity in the marketplace by one year, and even to transfer this period of exclusivity to another pharmaceutical or biologic in order to help offset the costs of research and testing of new products for neonates.

While lobbying efforts for the needs of sick and aging adults are heavily funded, neonates cannot lobby or advocate for themselves. We must recognize and respond to this unmet need and speak up for those who have no voice. Without our efforts on their behalf, many sick and preterm infants may never reach adulthood. **Therefore, the National Perinatal Association endorses S.2041 - Promoting Life-Saving New Therapies for Neonates Act of 2015 in the hopes that these long-neglected and vulnerable patients will be the recipients of therapeutic advances to improve their long-term survival and outcome.**

References:

(1) Carroll AE. $2.6 billion to develop a drug? New estimate makes questionable assumptions. New York Times, Nov. 18, 2014. (http://www.nytimes.com/2014/11/19/upshot/calculating-the-real-costs-of-developing-a-new-drug.html?_r=0).

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