Federal Legislation and the Advancement of Neonatal Drug Studies

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The directive from the US Congress, through laws and regulations mandating that manufacturers of pharmaceuticals demonstrate proof that new drugs are both safe and efficacious in target groups, has been in place for 50 years.[1,2] However, children and, in particular, neonates remain disproportionately underrepresented in the majority of drug clinical trials. To date, federal legislation has been slow to respond to the need for improvement in this regard, and it has only been in the last one and a-half decades that attempts have been made to rectify this unacceptable situation. Children remain therapeutic orphans, and it has taken the might of the federal government to include them in drug development processes.

The common practice of extrapolating data from studies conducted in adults and older children to neonates is problematic, even if the effects of the drugs and course of the disease are similar. Applicability of such data is limited by the unique physiology in neonates, an ever-changing body composition, rapid developmental processes, and a nonlinear relationship between body weight and pharmacologic variables. Dire consequences associated with the use of chloramphenicol (gray baby syndrome), sulfisoxazole and penicillin (kernicterus), novobiocin (hyperbilirubinemia), and vitamin E (neonatal sepsis and necrotizing enterocolitis) are some of the reminders of the danger of adopting therapies without adequate scientific information supporting the safety of the medications in the relevant populations.[3-8] This review assesses efforts by government agencies to extend the benefits of federal legislations pertaining to drugs administered to infants and children, applauds its successes, highlights areas where knowledge gap exists, and offers suggestions on where efforts need to be focused.

Legislative Efforts to Include Children in the Drug Development Process

In recognition of the paucity of children-specific pharmacologic data on medication prescribed to children, the federal government, through the National Institutes of Health and the Food and Drug Administration (FDA), have taken several steps toward generating new knowledge about medicines prescribed to children.[9,10] These resulted in the creation of the Pediatric Pharmacology Research Units (PPRU) Network, the FDA Modernization Act (FDAMA), the Best Pharmaceuticals for Children Act (BPCA), and the Pediatric Research Equity Act (PREA).[11-14] The PPRU Network, which comprised academic pediatric clinical pharmacologists at 13 sites, was initially organized in 1994 under the auspices of the National Institute of Child Health and Human Development (NICHD) to assist industry in performing drug-labeling studies in children. These units eventually morphed into multidisciplinary investigator groups including developmental biology, systems pharmacology, pharmacogenomics, biomarker development, and bioinformatics working to improve translational and clinical pediatric therapeutic studies despite the waning enthusiasm for funding.[15]

The FDAMA, enacted in 1997, was designed to create financial incentive for industry to conduct pediatric medication-labeling studies in children at the request of the FDA in return for accelerated approval process and an additional 6 months of market exclusivity. The original intent of the pediatric exclusivity program was to encourage research that enables the FDA to label drugs for appropriate use in children in the US, and it resulted in several pediatric label changes. Though the FDAMA expired in 2002, a similar impetus for pharmaceutical companies was sustained through the BPCA, which was enacted the same year. In addition, the BPCA has facilitated collation of an up-to-date compendium of prioritized drugs that need additional studies.[16] Unlike the BPCA, the PREA, enacted in 2003, requires pediatric studies for the indications for which sponsors are seeking approval in adults.

The FDAMA, BCPA, and the PREA have been credited with >400 pediatric drug-labeling changes since 1998.[17] Some of the reasons for such pediatric drug-label changes include expansion of approved ages for use (eg, topiramate, olopatadine, rocuronium), expanded indications from adults to pediatrics (eg, pantoprazole for gastroesophageal reflux, amoxicillin-clavulanate potassium for pneumonia, tenofovir for HIV infection), and new indications (eg, clonidine for attention-deficit disorder, mometasone for allergic rhinitis, pneumococcal 13-valent conjugated vaccine). It is anticipated that the success accrued by these programs would continue as result of the recent US congressional action to make these laws permanent.

BPCA	Best Pharmaceuticals for Children Act
FDA	Food and Drug Administration
FDAMA	FDA Modernization Act
NICHD	National Institute of Child Health and Human Development
PPRU	Pediatric Pharmacology Research Unit
PREA	Pediatric Research Equity Act

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Drug Clinical Trials in Neonates

Although pediatric drug-labeling studies as a whole have increased substantially as a result of governmental measures, there remain several notable shortfalls. Less than 6% of the 424 label changes have involved neonates.[17-19] This quandary is underscored by the fact that of the >120 000 studies currently at the National Institutes of Health clinical trials repository (clinicaltrials.gov), only 0.6% involve neonates, and only 3.4% of all pediatric studies registered involve neonatal pharmacologic therapeutic trials.[20] Indeed, this dearth of representation implies that neonates constitute a "therapeutic orphan," potentially placing them at substantial risk for receiving ineffective medications, dosing that is not validated, and for developing unanticipated complications such as adverse drug reactions.[21-24]

Outside of academia, minimal effort has been made to address the distinct pharmacokinetic and pharmacodynamic differences between neonates and older children. In the current legislations and regulations, these 2 populations have always been lumped together. Yet, we recognize that premature infants are not just miniature children or adults. The inherent differences are a consequence of body composition, various physiologic adaptations, the evolving ontogeny of abundance and responsiveness of receptors, and the function of drug-metabolizing enzymes and known transporters. Dynamic physiologic changes occur in neonates secondary to rapid growth and development that are manifested as postmenstrual and chronologic age-dependent alterations in absorption, distribution, metabolism, and excretion of drugs and their metabolites compared with older children and adults.[25,26] These disparities are particularly accentuated in the lowest birth weight strata.[27] For instance, the total body water composition in preterm infants (85%) is substantially higher than that of term infants (75%) and 6-month-old children (70%). When combined with the slower metabolism rates of premature infants, we find that the half-life of morphine, which is highly hydrophilic, varies from 9 hours in a preterm infant to 3-5 hours in a 6-month-old. The aforementioned differences need to be thoughtfully considered to engender meaningful changes in the current system.

The failure to appreciate and study neonates as a separate special population has resulted in extensive off-label and unapproved prescriptions, a practice that is most pronounced in the care of the critically ill neonates.[28-31] Although the terms "off-label" and "unapproved" are often viewed in the literature and in clinical practice as interchangeable, they are fundamentally different. For clarification, off-label prescription refers to FDA-approved drugs used for indications outside the FDA specifications. In contrast, an unapproved prescription refers to use of a FDA-approved drug in unapproved formulations (eg, medications compounded by pharmacies). The degree of prescription of off-label or unapproved drugs in the newborn intensive care units was largely unrecognized until the interrogation of a large national database demonstrated that 409 different drugs were prescribed over a 10-year period.[31] The true dilemma becomes thorny when prescription practices that are non–evidence-based are adopted as standard of care without proof of efficacy and safety, thereby undermining equipoise, engendering substantial ethical conundrums to future study, and sometimes effectively eliminating the ability to conduct appropriate placebo-controlled comparison trials. Many of these issues were highlighted in a recent report of the Institute of Medicine.[32] Without clinical trials, the safety profile of these off-label drugs prescribed to neonates is uncertain and could place them at substantial risk for unanticipated complications.

Obstacles to the Advancement of Drug Studies in Neonates

Several practical factors combine for the lack of enthusiasm about extending clinical trials to neonates. First, clinical trials in pediatrics are more cumbersome as children and neonates are considered a vulnerable group, necessitating additional regulatory burdens for drug trials. Second, many diseases affecting neonates have no equivalent in adults from which to garner basic pharmacologic information from Phase I trials. Third, rapid physiologic changes occurring in the first few months of life, manifested as altered pharmacodynamics in target groups, often lead to studies with incorrect assumptions when extrapolating adult data, imprecise outcome measures, and inadequate biomarkers or surrogates for efficacy. Additionally, the traditional control trial design, especially for the extremely premature (23- to 27-week postmenstrual age) infants, is often not feasible.

Financial disincentives also contribute to the lack of enthusiasm about the development of drugs for neonatal indications. The incidence of neonatal diseases is relatively low, making enrollment tedious and rendering some studies impractical or impossible. Additionally, prevailing drug development models emphasize large market effects, making economic feasibility unrealistic. To illustrate the magnitude of the problem with drugs targeted to neonates, clopidogrel is prescribed to nearly 48 million people worldwide and netted the manufacturer, Sanofi, approximately $9 billion in sales in 2010. In contrast, poractant alfa, a "blockbuster drug" prescribed to neonates as replacement therapy for respiratory distress syndrome, is estimated to have reached $275 million in international sales over the same time period. Consequently, well-intentioned physicians, in an attempt to enhance patient care, empirically prescribe FDA-approved drugs off-label to neonates once efficacy has been established in adults without recognizing that the disposition and metabolism of drugs are not only predicated solely on the body size but also on the maturation of the enzyme system(s) and drug targets. This practice could be potentially harmful or even deadly because the preservatives and additives (eg, ethanol, benzyl alcohol, diethylene glycol, propylene glycol, polysorbate) used commonly in medications intended for adults could be unsafe in neonates.