Published in final edited form as:
*J Pediatr*. 2013 January ; 162(1): 12–15. doi:10.1016/j.jpeds.2012.08.034.

# Federal Legislation and the Advancement of Neonatal Drug Studies

**Jason R Wiles, MD**[1], **Alexander A Vinks, PharmD, PhD**[2,3], and **Henry Akinbi, MD**[1,3]

[1]Perinatal Institute, Division of Neonatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

[2]Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

[3]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

**Keywords**

neonates; drug safety; drug efficacy; therapeutic orphan; pediatric labeling; Food and Drug Administration; Best Pharmaceuticals for Children Act; Pediatric Research Equity Act; National Institute of Child Health and Human Development

The directive from the United States 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 non-linear 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,



Corresponding Author: Henry Akinbi, M.D., Cincinnati Children's Hospital Medical Center, Division of Neonatology, 3333 Burnet Ave, MLC 7009, Cincinnati, OH 45229-3039, henry.akinbi@cchmc.org, phone: (513) 636-8918, fax: (513) 636-7868.



The authors declare no conflict of interest.

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 Institute of Health (NIH) and the Food and Drug Administration (FDA), have taken several steps towards 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 six 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 over 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 (e.g. topiramate, olopatadine, rocuronium); expanded indications from adults to pediatrics (e.g. pantoprazole for gastroesophageal reflux, amoxicillin/clavulanate potasium for pneumonia, tenofovir for HIV infection); and new indications (e.g. 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 United States congressional action to make these laws permanent.

## 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 over 120,000 studies currently at the NIH 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 two 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 when 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 afore-mentioned differences need to be thoughtfully considered in order 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 (e.g. medications compounded by pharmacies). The degree of prescription of off-label or unapproved drugs in the Newborn Intensive Care Units (NICU) was largely unrecognized until the interrogation of a large national database demonstrated that 409 different drugs were prescribed over a ten-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 post-menstrual 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, Plavix (clopidogrel) is prescribed to nearly 48 million people worldwide and netted the manufacturer, Sanofi, approximately $9 billion in sales in 2010. In Contrast, Curosurf (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 is not only predicated solely upon 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.

## OVERCOMING HURDLES TO DRUG LABELING STUDIES IN NEONATES

Undeniably, many medications that were never studied in neonates have contributed to improved outcomes and have played a role in extending the limit of viability in infants born prematurely. Juxtaposed to these successes, however, is a history replete with accounts of the potentially devastating consequences when therapies are adopted without systematic investigation, supporting the call for better evidence-based practice. A laudable step toward rectifying this unacceptable situation was through the establishment of the NICHD-sponsored Pediatric Trials Network. This is an alliance of clinical research sites developed to provide an infrastructure suited for the advancement of pediatric drug-labeling for off-patent drugs that are considered critical [33].

Additionally, challenges to conducting drug-labeling studies in neonates could be overcome by involving pediatric clinical pharmacologists and neonatologists from academia early in the process of study design to spur innovation and enhance practical utility of the data. This multidisciplinary research approach would promote thoughtful anticipation, careful planning to identify and eliminate barriers, and utilization of novel investigative practices to maximize the yield of individual studies [34–36]. These ever-improving methods include careful analysis of applicable data from studies in adults, allometric scaling and use of physiologically-based pharmacokinetic modeling (*in silico* models), and thoughtful extrapolation from pharmacogenomics data [35, 37–41]. Efforts to apply these methodological principles were first realized as part of the PPRU initiatives and are now sustained in many pharmaceutical companies, due in large part to the European Medicines Agency (EMA) requirement for a Pediatric Investigational Plan (PIP) upon completion of Phase I trial. The PIP is a development plan required of manufacturers to extend understanding the pharmacology of drugs to the pediatric population. It includes a description of future pediatric studies and anticipated adaptations of the formulations for children. In addition, drug manufacturers must account for all age groups from birth to adolescence and define a timeline for when the studies will be conducted.

## DISCUSSION

There is a shared onus of responsibility to provide neonates with access to therapeutic agents that have been adequately studied. So far, efforts by governmental agencies have been modestly successful, but fall short of the desired goal of including infants in drug clinical

trials in order to enhance safer use of medications in neonates. This special patient population needs to receive additional attention with the resources that are currently available, a position that was recently corroborated by the American Academy of Pediatrics' Committee on Drugs in a statement to the U.S. Congress and echoed by the Institute of Medicine [32, 42]. Drug manufacturers must proactively seek opportunities to study therapeutics in neonates in addition to older children, pursue neonatal studies earlier in the development process, and hold themselves accountable for conducting high quality studies. The FDA must continue to raise the standard for what is accepted as a sufficient study in neonates, provide guidance to pharmaceutical industries that demonstrate interest in expanding neonatal labeling studies, streamline regulatory requirements to minimize undue obstacles and delays to proposed studies, and reduce the burden on neonatal research participants by encouraging the use of population-based pharmacokinetic-pharmacodynamic studies [43]. Government must continue to provide financial incentives for industry, adequately fund priority studies, and support the training of practitioners in the principles of pharmacologic study in neonates. Practicing clinicians must temper enthusiasm to adopt unproven treatment modalities and look for opportunities to partner with pharmaceutical companies.

If studies in this special population are to be successful, we must also advance communication through transparency and the cooperative sharing of data between industry and academia. Involving experts in neonatal clinical pharmacology in the design and conduct of clinical trials would undoubtedly enhance the yield of these studies. The reauthorization of BPCA and PREA provides an opportunity for the FDA to improve the effectiveness of these two critical laws by ensuring that neonates are considered a unique group from other children. Resources should be channeled towards careful evidence-based practice, preferably through clinical trials of medication and biologic therapeutics, with the intent to maximize benefits and reduce the likelihood and severity of adverse outcomes. After all, we all agree to first do no harm - *Primum Non Nocere*.

## Acknowledgments

The authors would like to thank George P. Giacoia, MD (medical officer in the Obstetric and Pediatric Pharmacology Branch at the NICHD), for his insightful comments during the early stages of this manuscript.

J.W, is supported by National Institutes of Health (1T32HD069054 to Cincinnati Children's Hospital Medical Center; PI is A.V.).

## Abbreviations

| | |
|---|---|
| **NIH** | National Institute of Health |
| **FDA** | Food and Drug Administration |
| **NICHD** | National Institute of Child Health and Human Development |
| **FDAMA** | FDA Modernization Act |
| **PPRU** | Pediatric Pharmacology Research Units |
| **BPCA** | Best Pharmaceuticals for Children Act |
| **PREA** | Pediatric Research Equity Act |
| **PIP** | Pediatric Investigational Plan |

## REFERENCES


1. Avorn J. Learning about the safety of drugs--a half-century of evolution. N Engl J Med. 2011; 365:2151–2153. [PubMed: 22150034]
2. U.S. Congress. Washington: GPO; 1962. Drug Amendments of 1962; p. 76Public Law 87–781.
3. Sutherland JM. Fatal cardiovascular collapse of infants receiving large amounts of chloramphenicol. AMA J Dis Child. 1959; 97:761–767. [PubMed: 13649107]
4. Andersen DH, Blanc WA, Crozier DN, Silverman WA. A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. Pediatrics. 1956; 18:614–625. [PubMed: 13370229]
5. Sutherland JM, Keller WH. Novobiocin and Neonatal Hyperbilirubinemia: An Investigation of the Relationship in an Epidemic of Neonatal Hyperbilirubinemia. Archives of Pediatrics and Adolescent Medicine. 1961; 101:447.
6. Johnson L, Bowen FW Jr, Abbasi S, Herrmann N, Weston M, Sacks L, et al. Relationship of prolonged pharmacologic serum levels of vitamin E to incidence of sepsis and necrotizing enterocolitis in infants with birth weight 1,500 grams or less. Pediatrics. 1985; 75:619–638. [PubMed: 3885152]
7. Yaffe SJ. Antibiotics for the newborn infant; a discussion of dosages. Clin Pediatr (Phila). 1965; 4:639–643. [PubMed: 4284791]
8. Robertson AF. Reflections on errors in neonatology: II. The "Heroic" years, 1950 to 1970. J Perinatol. 2003; 23:154–161. [PubMed: 12673267]
9. Giacoia GP, Birenbaum DL, Sachs HC, Mattison DR. The newborn drug development initiative. Pediatrics. 2006; 117:S1–S8. [PubMed: 16777817]
10. Giacoia GP, Mattison DR. Selected Proceedings of the NICHD/FDA newborn drug development initiative: Part II. Clin Ther. 2006; 28:1337–1341. [PubMed: 17062307]
11. U.S. Congress. Washington: GPO; 1997. Food and Drug Administration Modernization Act of 1997; p. 111Public Law 105–115.
12. U.S. Congress. Washington: GPO; 2002. Best Pharmaceuticals for Children Act; p. 115Public Law 107–109.
13. U.S. Congress. Washington: GPO; 2003. Pediatric Research Equity Act of 2003; p. 117Public Law 108–155.
14. Ward RM, Kauffman R. Future of pediatric therapeutics: reauthorization of BPCA and PREA. Clin Pharmacol Ther. 2007; 81:477–479. [PubMed: 17375103]
15. U.S. National Institutes of Health. Pediatric Pharmacology Research Units (PPRU) Legacy. Available from: http://ppru.org.
16. U.S. Food and Drug Administration. [Accessed December 29, 2011] Best Pharmaceuticals for Children (BPCA) Priority List of Needs in Pediatric Therapeutics. Available from: http://bpca.nichd.nih.gov/about/process/upload/2011_Priority_List_and_Summary_for_web_posting_04_07_11.pdf.
17. U.S. Food and Drug Administration. [Accessed December 29, 2011] Pediatric Exclusivity Labeling Changes. Available from: http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM163159.pdf.
18. Ward RM, Kern SE. Clinical trials in neonates: a therapeutic imperative. Clin Pharmacol Ther. 2009; 86:585–587. [PubMed: 19915600]
19. James L, Ito S. Neonatal pharmacology: rational therapeutics for the most vulnerable. Clin Pharmacol Ther. 2009; 86:573–577. [PubMed: 19915596]
20. U.S. National Institutes of Health. ClinicalTrials.gov Registry. Available from: www.clinicaltrials.gov.
21. Shirkey H. Therapeutic orphans. J Pediatr. 1968; 72:119–120. [PubMed: 5634934]
22. Mitchell AA, Goldman P, Shapiro S, Slone D. Drug utilization and reported adverse reactions in hospitalized children. Am J Epidemiol. 1979; 110:196–204. [PubMed: 463874]
23. Kumar S. Adverse drug reactions in the newborn. Annals of clinical and laboratory science. 1985; 15:195. [PubMed: 2986513]

24. Mason J, Pirmohamed M, Nunn T. Off-label and unlicensed medicine use and adverse drug reactions in children: a narrative review of the literature. Eur J Clin Pharmacol. 2012; 68:21–28. [PubMed: 21779968]
25. Johnson PJ. Neonatal pharmacology--pharmacokinetics. Neonatal Netw. 2011; 30:54–61. [PubMed: 21317099]
26. Yokoi T. Essentials for starting a pediatric clinical study (1): Pharmacokinetics in children. J Toxicol Sci. 2009; 34(Suppl 2):SP307–SP312. [PubMed: 19571484]
27. Sonnier M, Cresteil T. Delayed ontogenesis of CYP1A2 in the human liver. Eur J Biochem. 1998; 251:893–898. [PubMed: 9490065]
28. Choonara I, Conroy S. Unlicensed and off-label drug use in children: implications for safety. Drug Saf. 2002; 25:1–5. [PubMed: 11820908]
29. t Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, van den Anker JN. Unapproved and off-label use of drugs in a children's hospital. N Engl J Med. 2000; 343:1125. [PubMed: 11032528]
30. Barr J, Brenner-Zada G, Heiman E, Pareth G, Bulkowstein M, Greenberg R, et al. Unlicensed and off-label medication use in a neonatal intensive care unit: a prospective study. Am J Perinatol. 2002; 19:67–72. [PubMed: 11938479]
31. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Reported medication use in the neonatal intensive care unit: data from a large national data set. Pediatrics. 2006; 117:1979–1987. [PubMed: 16740839]
32. Institute of Medicine. The National Academies Press; 2012. Safe and Effective Medicines for Children: Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act.
33. U.S. National Institutes of Health. Pediatric Trials Network. Available from: http://pediatrictrials.org.
34. Giacoia GP, Mattison DR. Newborns and drug studies: the NICHD/FDA newborn drug development initiative. Clin Ther. 2005; 27:796–813. [PubMed: 16117987]
35. Field, MJ.; Behrman, RE., editors. Committee on Clinical Research Involving Children. Ethical Conduct of Clinical Research Involving Children. Washington (DC): Ethical Conduct of Clinical Research Involving Children; 2004.
36. Ward RM, Benitz WE, Benjamin DK Jr, Blackmon L, Giacoia GP, Hudak M, et al. Criteria supporting the study of drugs in the newborn. Clin Ther. 2006; 28:1385–1398. [PubMed: 17062311]
37. U.S. Food and Drug Administration. [Accessed December 15, 2011] Guidance for Industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications. Available from: www.fda.gov/downloads/Drugs/GuidanceCompianceRegulatoryInformation/Guidances/ucm072109.pdf.
38. Rowland M, Peck C, Tucker G. Physiologically-based pharmacokinetics in drug development and regulatory science. Annu Rev Pharmacol Toxicol. 2011; 51:45–73. [PubMed: 20854171]
39. Leeder JS. Developmental pharmacogenetics: a general paradigm for application to neonatal pharmacology and toxicology. Clin Pharmacol Ther. 2009; 86:678–682. [PubMed: 19865080]
40. Cella M, Zhao W, Jacqz-Aigrain E, Burger D, Danhof M, Della Pasqua O. Paediatric drug development: are population models predictive of pharmacokinetics across paediatric populations? Br J Clin Pharmacol. 2011; 72:454–464. [PubMed: 21501213]
41. Mouksassi M, Marier J, Cyran J, Vinks A. Clinical trial simulations in pediatric patients using realistic covariates: application to teduglutide, a glucagon-like peptide-2 analog in neonates and infants with short-bowel syndrome. Clinical Pharmacology & Therapeutics. 2009; 86:667–671. [PubMed: 19847163]
42. Energy and Commerce Committee, Health Subcommittee, 112th Congress. 2nd Sesson ed.. Washington: Testimony of Daniel Frattarelli; 2012. Hearing on Reauthorization of PDUFA: What It Means for Jobs, Innovation, and Patients.
43. Vinks AA. Important role of population pharmacokinetic/pharmacodynamic modeling in pediatric therapeutics. J Pediatr. 2011; 159:361–363. [PubMed: 21764403]