Published in final edited form as:

Curr Pharm Des. 2017 ; 23(38): 5801–5804. doi:10.2174/1381612823666170926114857.

Collaboration in Regulatory Science to Facilitate Therapeutic Development for Neonates

Susan K. McCune^{1,*}, Yeruk Ager Mulugeta², and Gerri R. Baer¹

¹Office of Pediatric Therapeutics, Office of the Commissioner, Food and Drug Administration

²Division of Pediatric and Maternal Health, Center for Drug Evaluation and Research, Food and Drug Administration

Abstract

Background—Historically, neonatal therapeutic interventions were derived from adult therapeutics, and tragedies resulting from this approach have demonstrated differences in the pathophysiologic and developmental processes between neonates and older patients. Over the past 3 decades, researchers and collaborative research networks have made progress in the systematic evaluation of neonatal therapies, yet most neonatal therapeutic products have been incompletely assessed for safety and efficacy, and remain unlabeled and unapproved.

Approach—This work describes the legislative initiatives that have stimulated an increase in pediatric and neonatal studies. It highlights examples of successful neonatal drug studies that have resulted in informative neonatal labeling changes, as well as studies that have produced incomplete information. Strategies that support the design of successful studies, including targeting specific subpopulations, modeling and simulation to inform dose selection, innovative design strategies, biomarkers, and endpoints are discussed. Multi-stakeholder consortia such as the International Neonatal Consortium (INC), are working to improve the tools needed for the development of neonatal therapies. These research tools may be used by trial networks to inform consistent and efficient multicenter studies.

Conclusion—More data are needed to support safe and effective use of drugs in neonates, and to obtain these data, a thorough understanding of pathophysiology, drug disposition, biomarkers, and clinically-meaningful endpoints is required. This information will be derived from clinical trials, registries, real-world evidence, and the medical literature. Collaboration of consortia and the development of research networks are essential to achieving these goals.

* Address correspondence to this author at the Office of Pediatric Therapeutics, Office of the Commissioner, Food and Drug Administration; Tel: 301-796-8659; Fax: 301-847-8640; susan.mccune@fda.hhs.gov.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

DISCLAIMER: The above article has been published in Epub (ahead of print) on the basis of the materials provided by the author. The Editorial Department reserves the right to make minor modifications for further improvement of the manuscript.

1. BACKGROUND

While the field of neonatology is only a little over 50 years old, therapeutic intervention for neonates began in the 18th century with the first use of oxygen for neonatal resuscitation. For almost 250 years, neonatologists have been struggling to identify the optimal use of oxygen in neonates, one that promotes survival without worsening long-term outcomes such as neuronal injury in hypoxic-ischemic encephalopathy or retinal vessel proliferation in retinopathy of prematurity.[1,2] In the early years of neonatology, treatment of neonates with new therapeutics based on adult information resulted in kernicterus from sulfisoxazole prophylaxis, grey-baby syndrome from chloramphenicol treatment, brain lesions from hexachlorophene bathing, and gasping syndrome associated with exposure to benzyl alcohol. [2] These examples demonstrate the particular vulnerabilities of the neonate, and the fundamental need to understand the underlying pathophysiology of neonatal disease and the ontogeny of organ and enzyme systems required for the absorption, distribution, metabolism, and elimination of drugs in neonates. This information will provide the basis for modeling and simulation of appropriate doses of drugs. These doses would then be used in innovative clinical trial designs using biomarkers and clinical outcome assessment tools to provide clinically meaningful short-, medium- and long-term trial endpoints. This approach would be used to establish the safety and efficacy of therapeutic products used to treat neonates.

Neonatal Intensive Care Units (NICUs) have often functioned in silos with little collaboration and a broad range in standard of care. The NICHD Neonatal Research Network, which was established in 1986, is one of the largest collaborations between neonatal academic centers and NICHD. Currently, the Neonatal Research Network includes 15 academic centers, which is a small percentage of the total number of neonatal academic centers in the U.S. and does not include non-academic NICUs. Studies done at single centers outside a network may include input from other stakeholders, including parents, but they are frequently stand-alone efforts at individual institutions that are able to enroll only a small number of patients. In order to achieve labeling of therapeutic products for neonates, it is critically important that the neonatology community (academic institutions, private centers, industry, patient/parent advocacy groups, and government agencies) collaborate through consortia to generate the individual pieces of the puzzle to ultimately provide safe and effective therapeutics for neonates.

2. DRUG STUDIES IN NEONATES

Over the past 50 years, multiple drugs and biologics (referred to as drugs) have been used to treat neonates. The majority of these have been used off-label, which means that the dosing, safety and effectiveness of these drugs have not been adequately studied in the neonatal population in order to provide labeling for use in that population. Examples of drugs that have been approved for treatment of neonates include nitric oxide for use in term infants, surfactants, and caffeine. Studies have reported that infants <28 weeks gestation are exposed to a mean of 12 drugs during their hospitalization [3], with 93% of neonates receiving at least one off-label medication during their hospitalization [4].

Legislative mandates have stimulated pediatric and neonatal studies. In 1997, Congress passed pediatric legislation under the Food and Drug Administration Modernization Act. This was followed by the Best Pharmaceuticals for Children Act (BPCA) in 2002 and the Pediatric Research Equity Act (PREA) in 2003. Both BPCA and PREA were made permanent under the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012.[5] FDASIA requires that written requests under BPCA must provide a rationale for not including neonates in the pediatric studies, and that a report on efforts to increase neonatal product development be submitted to Congress every 5 years. There is also a mandate for neonatology expertise within the Office of Pediatrics in the Office of the Commissioner and on the Pediatric Review Committee at FDA.[6] Dr. Gerri Baer, a neonatologist, is a member of the Office of the Pediatric Therapeutics, and the new director of the Office of Pediatric Therapeutics is also a neonatologist.

These legislative mandates have resulted in a number of studies in neonates. Some of the studies have resulted in specific labeling information for use in neonates while other studies have not resulted in sufficient information to establish efficacy and safety in neonates. While progress is being made with respect to information in labels specifying drug use in neonates, one concern is that parts of the legislation may be promoting the study of drugs in neonates that are not actually being used in NICUs.[7]

New neonate-specific therapies are infrequently developed and approved, and many drugs are still used off-label in the NICU. With respect to studies that were not able to establish safety and effectiveness in the neonatal population, it is not clear whether the drugs actually are not efficacious in neonates or whether the trial design contributed to the negative outcome of the studies. To optimize the chance for success of a neonatal trial, participants need to be enrolled and treated with the correct dose, for the correct length of time, with measurement of correct endpoints. Examples of specific issues related to labeling for neonatal studies will be discussed below.

Of the studies that were performed to support new neonatal labeling, many involved both PK and safety/efficacy studies while others provided PK and safety data. The approach to perform PK and safety studies alone was based on a determination that the disease was sufficiently similar in the neonatal population so that efficacy could be extrapolated from data in older children and/or adults. The PK and safety studies have resulted in important dosing information for the neonatal population, highlighting the maturational changes that alter absorption, distribution, metabolism, and excretion (ADME) of drugs. An example of this is the meropenem label, which states, "Use of MERREM I.V. in pediatric patients less than 3 months of age with intra-abdominal infections is supported by evidence from adequate and well-controlled studies in adults with additional data from a pediatric pharmacokinetic and safety study." [8]

Some studies have highlighted specific safety concerns that would preclude that drug being used in neonates. This is demonstrated in the spinosad label, which reads, "NATROBA Topical Suspension contains benzyl alcohol and is not recommended for use in neonates and infants below the age of 6 months. Systemic exposure to benzyl alcohol has been associated with serious adverse reactions and death in neonates and low birth-weight infants." [9]

Specific neonatal information about reduced drug clearance in neonates was reported for lamivudine. “Limited, uncontrolled pharmacokinetic and safety data are available from administration of lamivudine (and zidovudine) to 36 infants aged up to 1 week in 2 trials in South Africa. In these trials, lamivudine clearance was substantially reduced in 1-week-old neonates relative to pediatric subjects (aged over 3 months) studied previously. There is insufficient information to establish the time course of changes in clearance between the immediate neonatal period and the age-ranges over 3 months old.”[10]

In those studies of neonates where efficacy and safety could not be established, it is not clear whether the pathophysiological differences in disease in neonates, compared with adults or older children, were sufficiently well understood to support selection of critical trial design elements including dose and study endpoint. This is exemplified by the information in the clopidogrel label, “A randomized, placebo-controlled trial (CLARINET) did not demonstrate a clinical benefit of clopidogrel in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt. Possible factors contributing to this outcome were the dose of clopidogrel, the concomitant administration of aspirin and the late initiation of therapy following shunt palliation. It cannot be ruled out that a trial with a different design would demonstrate a clinical benefit in this patient population.”[11] Another example is the dexmedetomidine label which includes information about open label studies in neonates. “Safety and efficacy have not been established for Procedural or ICU Sedation in pediatric patients. One assessor-blinded trial in pediatric patients and two open label studies in neonates were conducted to assess efficacy for ICU sedation. These studies did not meet their primary efficacy endpoints and the safety data submitted were insufficient to fully characterize the safety profile of Precedex for this patient population.”[12]

In some cases, only small numbers of neonatal patients were included in much larger pediatric trials. An example of this is the rocuronium bromide label, “ZEMURON was also studied in pediatric patients up to 17 years of age, including neonates, under sevoflurane (induction) and isoflurane/nitrous oxide (maintenance) anesthesia. Onset time and clinical duration varied with dose, the age of the patient, and anesthetic technique.”[13] Twenty-one neonates were included in this study.

Investigators planning neonatal studies need to consider whether specific neonatal subpopulations should be included. In the neonatal population this could include 1 month old full term neonates alongside infants 28 weeks post-menstrual age (PMA), who were born at 24 weeks gestation and are 1 month postnatal age (PNA). ADME, disease pathophysiology, and concomitant illnesses/treatments may be sufficiently different in this heterogeneous population as to confound the results of the trial. Encouraging enrollment of more homogeneous populations in neonatal trials will be important to understanding a therapy’s true safety and efficacy in the target population. ADME are all affected by the ontogeny of multiple organ and enzyme/transport systems in the neonatal period. Once a preterm infant is born, the ontogenic expression of these systems is altered from the normal in utero trajectory. The effect of these changes is clearly reflected in the meropenem dosing schedule for neonates found in the meropenem label.

Modeling and simulation may help reduce the uncertainty around dose selection in neonates. While this will be an important approach, more information about the ontogeny of ADME in the neonate, particularly in preterm infants, is needed to inform these models. The basic science information related to maturational changes in drug absorption, distribution, metabolism, and elimination as well as improved understanding of the impact of neonatal pathological processes and treatment modalities on PK/PD are needed to refine neonatal PK models.

Trial design is critically important in neonatal studies and much can be learned from studies in rare disease pediatric populations. Randomized, double-blind placebo controlled trials are considered the gold standard for evaluating efficacy in clinical trials. When the numbers of available patients is low and the disease presentation is heterogeneous, it may be difficult to complete randomized controlled trials. Therefore, it is critical to consider alternative trial designs including n-of-1, crossover, and adaptive trial designs.[14] Outcome measures that are used in adults and older children may also not be measurable or relevant in the neonatal population. New measurement tools including biomarkers and clinical outcome assessments (COAs) will need to be developed and validated in the neonatal population. The anesthesia community has taken a unique approach to studying pain in infants. They discussed the use of small sample designs including cross-over trials and n-of-1 studies to evaluate pediatric pain, as well as analgesic PK differences in neonates from older populations. They recommended immediate-rescue paradigms using analgesic sparing as a primary surrogate endpoint for acute pain studies of efficacy and dose response.[15]

Finally, the data generated in neonates must be reproducible. This is especially true for ontogenic ADME data and the development of new neonatal biomarkers or COAs. Biomarker development programs must consider specimen handling issues, assay issues, and performance issues in the specific trial design. The bio-marker should be validated independent of its use to make decisions in a particular trial. A task force from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has provided the framework for developing Patient Reported Outcomes for children including establishing the content validity of the instrument in different pediatric age groups.[16]

Successful neonatal clinical trials require a better understanding of the pathophysiology and natural history of neonatal diseases, the ontogeny of ADME pathways, and the neonates' clinical response to treatments. No single entity will be able to accomplish these goals alone. In order to ensure there are safe and effective therapies for neonates, the neonatal research community needs to collaborate to answer key scientific questions. Development of neonatal therapeutics will require the careful crafting of innovative trial designs, new biomarkers, new outcome assessment tools, and clinically meaningful short- and long-term endpoints. Network sites will need to be developed and supported by shared infrastructure with interoperable systems, standardized data, and standardized case report forms. All of this work can only be done through collaborative efforts. One model for this is the development of public-private partnerships or consortia that bring together stakeholders from academia, industry, patient/parent advocacy groups, regulators, and other government entities. In October, 2014, a workshop sponsored by the Critical Path Institute (CPath), Burroughs-Wellcome Fund, and the FDA was held at the FDA to discuss the logistics to support a

neonatal consortium.[17] Based on this initial meeting, the International Neonatal Consortium (INC) was launched in May 2015 at a workshop in London. In its first year, the INC focused on 4 key areas: clinical pharmacology, seizures, bronchopulmonary dysplasia (BPD), and databases. The clinical pharmacology working group produced a white paper addressing general clinical pharmacology considerations for conducting studies in term and preterm neonates.[18] The neonatal seizure working group has completed a master protocol for future clinical trials of therapies to treat neonatal seizures, with a focus on inclusion/exclusion criteria, trial designs, endpoint selection, and primary and secondary outcome measures. The BPD working group is completing a white paper on consensus definitions to lay the groundwork for future trials. The data working group has been investigating the extent of global neonatal databases with information on biomarkers, laboratory values, and standardized variables with the potential to use data from electronic health records to support clinical trials. Additional issues that are being discussed by INC working groups are adverse event reporting in neonates, retinopathy of prematurity, hemodynamic adaptation, long-term outcome measures, and the development of a neonatal common protocol template. As of March 2017, there are 77 academic centers, 10 regulatory/government agency members, 8 industry partners, and 7 parent/patient advocacy groups collaborating in INC.

Another consortium working on neonatal issues is the International Life Sciences (ILSI) - Health and Environmental Sciences Institute (HESI) Developmental and Reproductive Toxicology (DART) Committee. HESI is a non-profit institution founded in 1989 as a global branch of ILSI as a forum to advance the understanding of scientific issues related to human health, toxicology, risk assessment, and the environment. ILSI-HESI DART is a multisector collaborative research effort to identify and explore nonclinical models to inform the efficacy and long-term safety of drugs as they apply to neonatal disease. The working groups are surveying established non-clinical neonatal disease models, identifying nonclinical models to inform efficacy and safety of neonatal drug therapy in neonatal specific conditions and physiology as it pertains to neonatal ADME, and reviewing case studies to highlight the uses of non-clinical data to inform the selection of safe starting doses for neonatal studies.

These consortia provide opportunities for the scientific community to work together to develop innovative trial designs, new biomarkers, new outcome assessment tools, and clinically meaningful short- and long-term endpoints. Ultimately, these products will provide the underpinnings of research protocols to study the safety and efficacy of therapeutics in neonates. Collaborative efforts are needed to support the infrastructure for the actual trials in neonates. A successful example of these collaborative efforts is the Pediatric Trials Network (PTN), an alliance of clinical research sites sponsored by NICHD and managed through the Duke Clinical Research Institute that has focused on conducting clinical trials to support studies of off-patent drugs prioritized by NICHD under BPCA. The PTN has worked to optimize operational efficacy in early phase neonatal trials through optimizing sampling and maximizing enrollment.[19] Additional examples of collaborative efforts to provide support for neonatal clinical trials are the National Institute for Health Research, Medicines for Children Research Network in the U.K., the European Network of Paediatric Research at the European Medicines Agency, the Innovative Medicines Initiative (IMI) which is a joint effort between the European Union and the European Federation of Pharmaceutical

Industries and Associations (EFPIA), and the Institute for Advanced Clinical Trials for Children in the U.S.

SUMMARY

The neonatal scientific community has established that more data are needed to support the safe and efficacious use of drugs in neonates. Important information is required to support these efforts, including a better understanding of both the pathophysiology of diseases and the ontogeny of ADME needed for dose selection for neonates. This information will be used to support clinical trial designs that take into account information that is available through the literature, real world evidence, historical controls, and registries. Collaborative efforts through consortia will provide this scientific knowledge to the trial networks that offer the infrastructure to support neonatal trials. New technology including the use of small blood volumes in validated assays will be important, and all trials should take advantage of opportunistic sampling whenever possible. It will also be important to more clearly define adverse events in the NICU setting. All of these collaborative efforts will be critical in the development of safe and effective therapies for neonates.

Acknowledgments

Declared none.

References

1. Saugstad OD. Why are we still using oxygen to resuscitate term infants? J Perinatol. 2010; 30:S46–S50. [PubMed: 20877407]
2. Philip AGS. The evolution of neonatology. Ped Res. 2005; 58:799–815.
3. Warrier I, Du W, Natarajan G, Salari V, Aranda J. Patterns of drug utilization in a neonatal intensive care unit. J Clin Pharmacol. 2006; 46:449–455. [PubMed: 16554453]
4. Conroy S, McIntyre J. The use of unlicensed and off-label medicines in the neonate. Semin Fetal Neonatal Med. 2005; 10:115–122. [PubMed: 15701577]
5. Bai JPF, Barrett JS, Burckart GJ, Meibohm B, Sachs HC, Yao L. Strategic biomarkers for drug development in treating rare diseases and diseases in neonates and infants. AAPS J. 2013; 15:447–454. [PubMed: 23334978]
6. Califf, RM. Best Pharmaceuticals for Children Act and Pediatric Research Equity Act: July 2016 Status Report to Congress. Available at: (<https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM509815.pdf>)
7. Laughon MM, Avant D, Tripathi N, Hornik CP, Cohen-Wolkowicz M, Clark RH, Smith PB, Rodriguez W. Drug labeling and exposure in neonates. JAMA Pediatr. 2014; 168:130–136. [PubMed: 24322269]
8. Meropenem Label. 2016. [cited 2017 March 15]; Available at: (https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/050706s0351bl.pdf)
9. Spinosad Label. 2014. [cited 2017 March 15]; Available at: (https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/0224081bl.pdf). Accessed March 2017
10. Lamuvidine Label. 2016. [cited 2017 March 15]; Available at: (https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020564s036,020596s0351bl.pdf)
11. Clopidogrel Label. 2011. [cited 2017 March 15]; Available at: (https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020839s0511bl.pdf)
12. Dexmedetomidine Label. 2016. [cited 2017 March 15]; Available at: (https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021038s0271bl.pdf)

13. Rocuronium Bromide Label. 2008. [cited 2017 March 15]; Available at: (https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020214s030lbl.pdf)
14. Augustine EF, Adams HR, Mink JW. Clinical trials in rare disease: challenges and opportunities. *J Child Neurol.* 2013; 28:1142–1150. [PubMed: 24014509]
15. Berde CB, Walco GA, Krane EJ, et al. Pediatric analgesic clinical trial designs, measures and extrapolation: report of an FDA Scientific Workshop. *Pediatrics.* 2012; 129:354–364. [PubMed: 22250028]
16. Matza LS, Patrick DL, Riley AW, et al. Pediatric patient-reported outcome instruments for research to support medical product labeling: report of the ISPOR PRO good research practices for the assessment of children and adolescents task force. *Value Health.* 2013; 16:461–479. [PubMed: 23796280]
17. McCune SK, Mulugeta YA. Regulatory science needs for neonates: a call for neonatal community collaboration and innovation. *Front Pediatr.* 2014; 2:1–3. [PubMed: 24459665]
18. Ward RM, Benjamin D, Barrett JS, Allegaert K, Portman R, Davis JM, Turner MA, the International Neonatal Consortium (INC). Safety, dosing, and pharmaceutical quality for studies that evaluate medicinal products (including biological products) in neonates. *Pediatr Res.* 2017; 81:692–711. [PubMed: 28248319]
19. England A, Wade K, Smith B, Berezny K, Laughon M, on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network Administrative Core Committee. Optimizing operational efficiencies in early phase trials: the Pediatric Trials Network experience. *Contemp Clin Trials.* 2016; 47:376–382. [PubMed: 26968616]

Recommended Meropenem for Injection, USP Dosage Schedule for Pediatric Patients Less Than 3 Months of Age with Complicated Intra-Abdominal Infections and Normal Renal Function

Age Group	Dose (mg/kg)	Dose Interval
Infants less than 32 weeks GA and PNA less than 2 weeks	20	Every 12 hours
Infants less than 32 weeks GA and PNA 2 weeks and older	20	Every 8 hours
Infants 32 weeks and older GA and PNA less than 2 weeks	20	Every 8 hours
Infants 32 weeks and older GA and PNA 2 weeks and older	30	Every 8 hours

There is no experience in pediatric patients with renal impairment.