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A Pediatric Research Imperative: Addressing Neonates in Drug Development Through Understanding Neonatal Clinical Pharmacology

An N. Massaro, MD; Elimika Pfuma Fletcher, PharmD, PhD; Rajanikanth Madabushi, PhD; Gerri Baer, MD; and Dionna Green, MD

Drug development in the neonatal population remains an unmet need in health care. While incentives and legislative mandates have had some impact on increasing drug development in pediatric patients, the advancement of neonatal therapeutics faces unique challenges. This review summarizes relevant regulatory history, clinical, pharmacological and ethical considerations that characterize the landscape of drug development in neonates. Research priorities and future directions for advancing safe and effective medicines for the vulnerable neonatal population are discussed.

ABBREVIATIONS BPCA, Best Pharmaceuticals for Children Act; BW, birthweight; ELBW, extremely low birth weight; FDA, US Food and Drug Administration; FDARA, FDA Reauthorization Act; FDASIA, FDA Safety and Innovation Act; GA, gestational age; LBW, low birth weight; LGA, large for gestational age; NICU, neonatal intensive care unit; PD, pharmacodynamic; PK, pharmacokinetic; PMA, postmenstrual age; PNA, postnatal age; PREA, Pediatric Research Equity Act; SEE, substantial evidence of effectiveness; SGA, small for gestational age; VLBW, very low birth weight

KEYWORDS drug development; neonate; pharmacology; preterm infant

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Introduction

Despite recent advances in pediatric drug development, progress towards adequate evaluation and labeling of drugs for use in the neonatal population continues to lag. The majority of medications used to treat critically ill infants in the neonatal intensive care unit (NICU), have not undergone systematic evaluation for safety and effectiveness in neonates.[1,2] This is problematic given the unique physiology and developmental processes that often preclude reliance on extrapolation of pharmacokinetic (PK) and clinical data from older children or adults to inform use in neonates.

Neonatal drug development programs are inherently challenging. The heterogeneity of the patient population, relative rarity of clinical conditions impacting neonatal patients, lack of consensus on disease definitions, variable approaches to measuring adverse events and outcomes, and ethical and cost considerations all contribute to difficulty in conducting trials in neonates. Nevertheless, prioritizing drug development in neonates is a pediatric research imperative to ensure access to safe and effective medications in this vulnerable population.

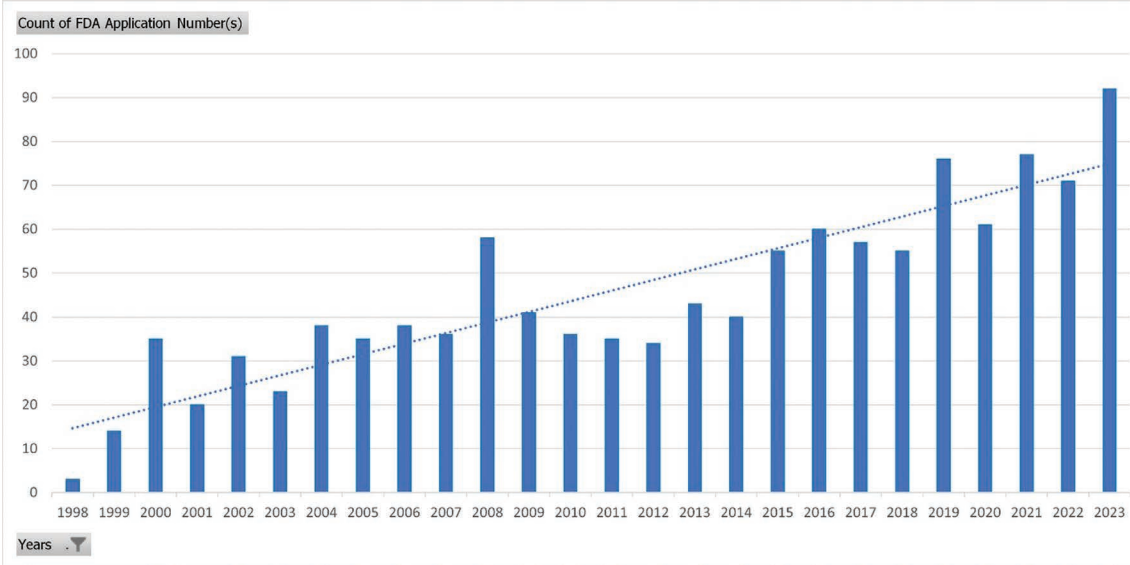
This paper will summarize the regulatory background and clinical considerations (including population-specific, clinical pharmacology and study design factors) that should be taken into account during neonatal drug development. Current gaps and future directions for advancing therapeutics in the neonatal population will be highlighted.

Regulatory History of Neonatal Product Development

In the United States, pediatric drug development is largely driven by pediatric-specific drug legislation. This includes the 2002 Best Pharmaceuticals Act for Children Act (BPCA),[3] which is the voluntary incentive program that allows for additional marketing exclusivity to be granted to drug developers who complete pediatric clinical studies as requested by the US Food and Drug Administration (FDA). Additionally, the 2003 Pediatric Research Equity Act (PREA)[4] gave FDA the authority to require pediatric studies for certain drug and biological products. Together these laws have led to a significant increase in number of pediatric studies conducted and a subsequent increase in the number of pediatric labeling changes for drugs and biologics over the past several decades (Figure 1).

In September 2022, FDA announced the historic milestone of achieving over 1000 medicines that include evidence-based pediatric information in product labeling.[5] This milestone represented the collaborative

Figure 1. Number of pediatric labeling changes for drugs and biologics pursuant to pediatric laws from 1998 to 2023.



effort of the FDA, federal partners, industry, researchers, patients/families, advocacy groups, and many other stakeholders who played an important role in informing the current approach to developing medicines for children. In 2023, the FDA issued 2 draft guidances to further promote public understanding of PREA and BPCA and their role in promoting drug development in pediatric patients.[6,7]

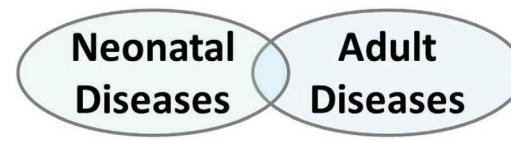
While BPCA and PREA have increased the number of pediatric labeling changes in general, the neonatal subpopulation remains understudied and largely unaddressed in product labeling. The majority of drugs to which neonates are exposed are used off-label. A recent review that evaluated product labeling pursuant to BPCA and PREA through 2021, found that of the 974 drugs with pediatric information in product labeling, less than 10% had labeling information pertaining to neonates and approximately 5% had an FDA-approved indication for neonatal use (Figure 2).

Figure 2. Labeling changes for neonates pursuant to Best Pharmaceuticals for Children Act and Pediatric Research Equity Act through 2023. Drugs may be labeled with information pertaining to use in neonates even if studies were not conducted in neonates. For example, drugs may be labeled with safety information based on non-clinical data.

There are several reasons why the current paradigm for drug development under PREA has generally not resulted in a significant increase in research addressing diseases and conditions in neonates. Drugs under development for adult conditions may not always be relevant for addressing the unique pathophysiology of the neonate and neonatal-specific conditions may not have an adult disease correlate. As PREA mainly addresses disease areas where there is commonality between adult and neonatal disease (Figure 3), a large proportion of neonatal diseases remain beyond the scope of the legislative mandate. Neonatal-specific diseases (e.g., complications of prematurity, hypoxic ischemic encephalopathy, persistent pulmonary hypertension of the newborn), in particular, require dedicated drug development efforts in neonates that can be challenging for many reasons as discussed in detail further below.

To address the lack of neonatal information in product labeling, there have been more recent provisions in legislation that have specifically pertained to the neonatal population. In addition to making BPCA and PREA permanent and requiring early planning of pediatric studies during drug development, the FDA Safety

Figure 3. Intersection between adult and neonatal diseases is limited.



and Innovation Act of 2012 (FDASIA) emphasized the need for increased neonatal studies. FDASIA includes provisions that require all BPCA exclusivity written requests to include a rationale for not including neonatal studies if none are requested, an increased number of FDA personnel with expertise in neonatology (including standing representation on the Pediatric Review Committee) and a report to Congress every 5 years regarding efforts to increase the number of neonatal drug development studies conducted. In the 2017 FDA Reauthorization Act (FDARA), the requirement for FDA to maintain personnel with neonatology expertise was made permanent and additional provisions included the need to issue neonatal-specific guidance. In June 2022, the FDA issued the first neonatal-specific guidance *General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products*[8] in response to this mandate. More recently, in October 2024 another guidance *Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development*[9] was issued.

Clinical Considerations for Neonatal Drug Development

There are many reasons for the limited study of drug products in neonates. These studies are inherently challenging, not only because the relative rarity of disease conditions in neonatal patients compared to adults, but also because of the added complexity of clinical factors that can impact evaluation of a drug administered to a neonate.[10–12] These factors include the rapid maturation of organs and tissues that occurs particularly during the third trimester of gestation, a period that occurs in the ex-utero environment for the preterm infant. Additionally, several organ systems, such as the kidneys and lungs, continue significant maturation after term birth into early infancy or childhood.[13] Developmental maturation at the cellular and biochemical level also represents a challenge as many enzymes, receptors, transporters, neurotransmitters and other signaling molecules are expressed differently with age.[14] Physiological changes associated with the transition from the in-utero to ex-utero environment after birth must also be considered as changes in circulation, oxygen tension, and function of organ systems such as the lungs and gastrointestinal tract are triggered after separation from placental support.[15] Finally, due to factors related to the overall immaturity of the neonate, and vulnerability across organ systems, assessment of safety and efficacy of a drug product may be particularly challenging to discern due to confounding effects of comorbid conditions.[16]

Definitions and Subgroup Classifications. Standardization of disease definitions and subgroup classifications is important for advancing neonatal drug development. Given the wide clinical heterogeneity that characterizes the neonatal population, using a common language can allow for methods to stratify patients based on characteristics that can greatly impact the analysis of PK and dose response data. This can allow for assurance that a product is evaluated across a range of gestational age (GA; age at birth dated from the first day of the mother's known or reported last menstrual period), postmenstrual age (PMA; age from the first day of the mother's known or reported last menstrual period), postnatal age (PNA; chronological age after birth) and birth weights (BWs) as appropriate. While these variables may be highly correlated (e.g., GA and BW), it is important to recognize that these characteristics differ conceptually and the information they provide is not necessarily interchangeable. GA/PMA reflects developmental maturity, PNA reflects transitional physiology which changes rapidly after birth, and BW impacts allometric scaling. Growth disturbances, including small for gestational age (SGA; less than 10th percentile BW for GA) or large for gestational age (LGA; greater than 10th percentile BW for GA), can also impact developmental physiology and pharmacology.

Consensus-based classification schemes include subgroups based on GA at birth: preterm neonates at the border of viability referring to neonates born at 22 to <24 weeks GA; extremely preterm neonates 24 to <28 weeks GA; very preterm neonates 28 to <32 weeks GA; moderate-to-late preterm neonates 32 to <3 weeks GA; term neonates 37 to <42 weeks GA; and post-term neonates ≥42 weeks GA at birth. Classifications based on BW include extremely low birth weight (ELBW) neonates born at <1000 g; very low birth weight (VLBW) neonates (<1500 g); and low birth weight (LBW) neonates (<2500 g).[8]

Establishing Safety and Substantial Evidence of Effectiveness. Given the challenges that impact drug development in neonates, the regulatory standard of having two adequate and well-controlled studies to establish safety and substantial evidence of effectiveness (SEE)[17] of a drug product may not always be feasible for many neonatal conditions. In some cases, existing data in adults and older pediatric populations can be leveraged to support SEE, a concept referred to as pediatric extrapolation.[18] As noted previously, while there are some conditions that occur commonly between adults and neonates, the degree of overlap, and therefore the ability to extrapolate efficacy from other populations, may be limited. This is true when conditions occur exclusively in neonates or in conditions where the natural history or pathophysiology of the condition in neonates differs significantly from adults. The areas where extrapolation has been most successfully used to support SEE in neonates are in anti-infective and antiviral drugs.[18] While a detailed framework regarding how pediatric extrapolation can be used to optimize neonatal drug development is beyond the scope of this review, it is noted that draft

guidance from the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) has been recently issued on pediatric extrapolation.[19] Given the difficulties with conducting large-scale efficacy trials and using extrapolation approaches in neonates, incorporation of novel methods to improve trial efficiency are needed. For example, biomarkers that can serve as appropriate measures of drug response can advance investigation of neonatal therapeutics, especially in conditions were evidence of efficacy may not be discernable until days, months and even years after treatment. The use of biomarkers or surrogate endpoints in neonatal specific indications are limited by a lack of validated surrogate endpoints.[20] Biomarker discovery and qualification have been incorporated into recent prospective, longitudinal clinical trials with the goal to develop surrogate endpoints for future studies (e.g., high-dose erythropoietin for asphyxia and encephalopathy [HEAL] trial).[21,22]

Regardless of the approach to establishing SEE, safety data should be obtained for all drugs studied in neonates. The size of the safety database needed depends on several factors including experience with the drug itself or similar drugs in adults, older children, or previously studied neonatal subpopulations, the seriousness (and frequency) of adverse reactions observed in other populations, the rarity of the condition, and the potential for unique susceptibility of the neonate to particular adverse events. For example, because of neurodevelopmental considerations, it may be recommended to follow neonates for potential safety issues longer than for older children and adults, especially if the drug is known to cross the blood brain barrier and be associated with high exposure to the developing brain. The approach to determining the need for long-term neurodevelopmental safety assessment for medical products being investigated in neonates is discussed in recent draft guidance issued by the FDA.[9] In evaluating safety during neonatal product development, consideration should be given to using neonatal-specific definitions for identifying and grading severity of adverse events.[23–25]

Clinical Pharmacology Considerations for Neonates

Information related to ontogeny (maturity) in neonates is still increasing. Pharmacokinetics, pharmacodynamics (PD), and potentially safety and efficacy differ in neonates compared with older pediatric and adult individuals due to ontogeny of body systems including those involved in absorption, distribution, metabolism and excretion of drugs. One unique aspect of neonatal PK is the significant maturation and growth that takes place within the neonatal period which results in PK differences and potentially dosing across the neonatal period. There is significant variability across neonates based on body size, conditions, and concomitant medications. In addition, ontogeny and therefore PK or PD can differ in term versus preterm neonates and across age (PMA and/or PNA).

The absorption of a drug is not only impacted by ontogeny factors in the gastrointestinal system or skin but can also be due to other factors such as the type of feeding and when feeding tubes are used. The distribution of the drug is impacted by body composition including fat and total body water composition and differences in protein and tissue binding. The elimination of a drug from the body can be impacted by maturity in drug metabolizing enzymes, transporters and renal function components such as glomerular filtration rate, reabsorption or secretion.[26]

Because of the variability in maturation and growth seen across the neonatal period, it is important to evaluate PK across a spectrum of PMA and PNA in the neonates. The maturation of various processes happens at different rates and therefore considerations can differ by drug. For example, raltagravir is metabolized by UGT1A1, an enzyme that undergoes rapid increases in activity after birth. In a study led by the IMPAACT network,[27] a cohort of neonates was dosed with two single doses of 3 mg/kg and modeling and simulation was used to inform dosing in a larger cohort of term neonates. Based on the model and knowledge of ontogeny the raltegravir mg/kg dose in the larger cohort was 1.5 mg/kg twice daily (BID) in Week 1, 3 mg/kg BID in Weeks 2 to 4 and 6 mg/kg BID in Weeks 5 to 6. This study informed weight band dosing in the various week periods within labeling for the drug.[28]

Ontogeny in target tissues may alter the PD and the PK/PD relationship. Therefore, PD can be analyzed in addition to PK in neonatal studies. PD can be measured by an effect on biomarkers or an early clinical endpoint. Identifying relevant PD endpoints can be challenging especially in scenarios where the disease or condition is specific to neonates and is not observed in adults. The FDA neonatal clinical pharmacology guidance recommends early discussion with FDA in considering relevant PD/biomarker for a study.[8]

In addition to PK and PD, pharmacogenomic assessments should be considered in neonatal studies. Pharmacogenomic effects on drug exposure and response have been reported for many drugs in adults and in some pediatric populations,[29] but the interplay of pharmacogenomics and ontogeny in aspects such as metabolic enzyme activity has not been fully elucidated. The impact of pharmacogenomics could differ in adults, older pediatrics and neonates. Therefore, the FDA recommends assessing pharmacogenomics within a neonatal study when pharmacogenomic differences for a drug are known or expected.[8]

Additional clinical pharmacology assessments specific for certain products are needed, such as

immunogenicity assessment for therapeutic proteins. Immunogenicity refers to the formation of anti-drug antibodies in response to certain treatments and can impact the PK, PD, safety or efficacy of some drugs. Immune responses can differ in neonates compares to older pediatrics and adults and this could result in differences in immunogenicity with drug treatment.[30]

Study Design Considerations

As previously discussed, it is important to ensure that studies are designed to include the spectrum of relevant clinical variability in the neonatal population of interest. In addition to ensuring adequate representation across subgroups, secondary subgroup analyses should be planned in order to assess whether findings differ amongst relevant subgroups. Considerations for designing clinical pharmacology studies and planning assessments include: Dose Selection, Formulation, Sample Size and PK Sampling and Analysis.

Dose Selection. All available relevant information should be used to inform the starting dose in neonates. Rapid growth and maturity during the neonatal period could mean dose adjustments within a short period of time. It is possible to consider studying different dosing regimens or incorporating innovative approaches such as dose titration, therapeutic drug monitoring and adaptive trial designs. These approaches can help provide the most robust information even in cases of a limited neonatal population for study. In many cases, clinical data are available from adults or older pediatric patients for drugs studied in neonates. However, if a novel treatment is developed for a neonatal-specific condition and a first in human study is being considered in a neonatal population, early discussion with regulatory agencies is warranted.

Important factors to consider in dose selection include age, whether the neonate is term or preterm, and body weight. For age, both PMA and PNA should be considered as the impact on dose can differ by drug and this has been highlighted by several drugs that are dosed using different criteria. The following are examples of drugs labeled for neonates that include various dosing approaches (Table).

Formulation. Age-appropriate formulations are needed for use in pediatric patients. This is especially challenging in neonates considering the low dosing volumes they may need due to low body weight, the range of dosing they may need over a short period of time, challenges in swallowing or using alternate dosage forms such as nasal or topical. From a safety perspective, careful consideration is needed related to the use of excipients including the volumes used.

Table. Approaches for Neonatal Dosing Related to Age

Drug Name	PMA	PNA	GA	Regardless of Age	Dosing Restrictions by Age
Acyclovir[42]	X				
Clindamycin	X				
Raltegravir[28]		X			
Ampicillin[43]		X	X		
Maraviroc[44]					Dosing only for term neonates >2 kg*
Technetium Tc99m Succimer					Dosing only for term neonates*
Rivaroxaban[45]					Dosing only if at least 37 weeks GA and ≥2.6 kg*
Ceftolozane and tazobactam[46]				*Dosing only if eGFR greater than 50 mL/min/1.73 m^2	
Lipid injectable emulsion[47]				X	
Nirsevimab				X (Dosing based on body weight categories)	

eGFR, estimated glomerular filtration rate; GA, gestational age; PMA, postmenstrual age; PNA, postnatal age

* Dosing is not recommended in certain categories (preterm, based on gestational age or eGFR value). The actual regimen proposed is not determined by age in the neonatal period

The amount of fluid volume load should be taken into account in the context of those that would be received from parenteral nutrition, enteral feeding and standard of care drugs in the population. In addition, certain excipients generally regarded as safe in older populations may have specific or increased safety concerns in neonates (e.g., ethanol, benzyl alcohol).

Sample Size. As noted above, it is important to include adequate numbers across various subpopulations of the neonatal populations (e.g., based on PMA or PNA). In addition, the sample size should consider variability needed for the relevant PK or PD endpoints. This may be challenging considering the relative rarity of specific neonatal conditions. In planning for a clinical pharmacology study, clinical trial simulations combining data from various sources can be used to inform the sample size.

PK Sampling and Analysis. Although the blood volume to weight ratio is higher in neonates compared to adults, the absolute blood volume of a neonate, and especially the preterm neonate, is small. Limitations of neonatal blood sampling need to be considered when designing clinical studies, especially when considering need for blood sampling for PK, PD, and laboratory safety monitoring within a study. Physiologic nadir, disease-associated and iatrogenic anemia may all contribute to the maximum amount of blood that can be drawn safely from pediatric patients for research purposes.[31] Blood sampling plans need to account for blood drawn for routine clinical assessments and ideally research-related blood draws should be timed with planned blood draws being performed for clinical purposes when possible. There exist opportunities to use scavenged blood samples which were collected for clinical use. However, such approaches require careful documentation, planning and accounting for storage conditions. Sparse sampling approaches are generally used in neonates to inform population PK modeling approaches. Careful consideration should be given to the sampling schedule and the number of samples required and this can be informed through clinical trial simulations.

In addition to the number of samples, the amount of blood collected should be carefully considered. Advances in analytical methods and technologies are allowing for smaller blood volumes. Therefore, alternative sampling methodologies such as microsampling (e.g., use of dried blood spots)can be considered.[32] In addition, alternative matrices such as urine can be incorporated. However bioanalytical validation best practices should be used to account for any bias in concentration compared to traditional blood sampling methodologies. The overall bioanalytical methods used should be accurate, precise, sensitive, specific and reproducible.[33]

Obtaining consent from parents during a stressful time and incorporating study procedures amongst the busy workflow for physicians and nurses represent other challenges to conducting studies in the NICU. Multi-stakeholder input early in the study design process, to ensure that studies are feasible and acceptable[34] to clinicians and families, is critical to trial success.

Modeling and Simulation to Support Neonatal Drug Development

Modeling and simulation approaches are important in pediatric drug development, including neonates, in informing study design, dosing and data analysis. Modeling approaches can allow for the integration of all available relevant information to inform use of a drug in neonates. Data and knowledge informing these models can include mechanism of action, ontogeny, PK and PD in adults and other pediatric populations. Modeling approaches can include population pharmacokinetic (pop PK), PK/PD, physiologically based pharmacokinetic and quantitative systems pharmacology modeling.[35] It has been reported that mechanistic-based approaches or allometric models that account for ontogeny or age-appropriate exponents are needed in pediatric patients < 2 years of age.[34]

An example of the application of modeling and simulation for neonatal dosing and approval is for maraviroc. Before approval in neonates, the drug was approved in adults and pediatric patients ≥ 2 years old based on available PK, PD, safety and efficacy data. The drug is a CYP3A substrate for which CYP3A inhibitors that are commonly co-administered in the indicated patient population can increase exposure. The clinical studies in those ≥ 2 years old included CYP3A inhibitors and allowed for dosing recommendations for those on inhibitors versus those not on inhibitors. The neonatal indication was supported by a phase 1 open label study in birth to 6 weeks of age using weight-based dosing, but no CYP3A inhibitors were used in the trial. Modeling and simulation were used to support dosing in those > 2 kg informed by study data with mg/kg dosing. In addition, the data from neonates and those ≥ 2 years of age were used to interpolate and provide dosing information for those between 6 weeks of age and 2 years of age for whom no studies were conducted. Modeling and simulation was proposed to support dosing with CYP3A inhibitors but the model was deemed insufficient due to uncertainty in the interplay with ontogeny in those <2 years of age.[36]

This maraviroc example demonstrates ways modeling and simulation can be used while highlighting the limitations in application based on current knowledge. The models rely upon understanding of developmental systems and ontogeny.[35] For example, good predictive performance has been reported for models for drugs that are predominantly renally eliminated in infants including neonates.[37] Although, we have increased

knowledge in ontogeny of various pathways, we still have limitations in our understanding of ontogeny including for some transporters.[38] Therefore, careful considerations are needed in informing our application of modeling.

Ethical Considerations. Generally, the pediatric population enrolled in a clinical trial of an investigational agent should have the disease or condition of interest, or in some cases be at risk for the disease or condition (i.e., studies cannot be performed in healthy children). Neonates exposed to a novel investigational agent must have a prospect of direct benefit from participating in a study.[39] This concept is governed by safeguards in place for clinical investigations in children, regulations commonly referred to as Subpart D.[40] The number of neonates exposed to the investigational product should be limited to the minimum sample size needed to achieve study aims. Other important ethical considerations include having neonatal expertise represented on the institutional review board of record reviewing the neonatal study protocol and the data safety and monitoring board tasked with monitoring safety during the trial. Details of these guidelines and other ethical regulations are beyond the scope of this review but have been outlined in recent guidance on ethical considerations for pediatric clinical studies.[41]

Future Directions

Advancing neonatal therapeutics will require addressing the many challenges discussed including clinical heterogeneity, dynamic nature of developmental disease and repair mechanisms, and vulnerability of the neonatal population. It is critical to understand the natural history of the disease/condition and identify biomarkers that can serve as appropriate measures of treatment response. Given the unique vulnerabilities and ethical considerations, multi-stakeholder input early in the study design process is essential to ensuring that patient-focused drug development is paramount to the overall investigative approach. Use of standardized disease definitions and classification schemes, emerging neonatal-specific drug development tools (e.g., Neonatal Adverse Event Severity Scale),[23–25] and careful consideration of available guidance documents[8,9,19,41] that pertain to neonatal drug development are important strategies for progress towards the overarching goal of comprehensive evaluation of safety and effectiveness for any and all medications administered to neonates.

Article Information

Affiliations. Office of Pediatric Therapeutics, Office of the Chief Medical Officer, Office of the Commissioner, US FDA (DG, ANM), Silver Spring, MD; Division of Hepatology and Nutrition, Office of New Drugs, Center for Drug Evaluation and Research, US FDA (GB), Silver Spring, MD; Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US FDA (EPF, RM), Silver Spring, MD.

Correspondence. An Massaro, MD; an.massaro@fda.hhs.gov

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