General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND 2

III. DEFINITIONS AND SUBGROUP CLASSIFICATIONS 3

IV. GENERAL CONSIDERATIONS 4

A. Pharmacokinetics 5

B. Pharmacodynamics 8

C. Pharmacogenomics 9

V. STUDY DESIGN CONSIDERATIONS 9

A. General Approaches to Providing Substantial Evidence of Safety and Effectiveness in Neonates 9

B. Study Population 10

C. Dose Selection 10

D. Formulation 11

E. Sample Size 12

F. Sampling 12

G. Bioanalytical Methods 15

H. Data Analysis 16

I. Clinical Study Report 18

J. Data Submission 18

K. Ethics 18

General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products Guidance for Industry[1]

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I. INTRODUCTION

This draft guidance is intended to assist sponsors of new drug applications (NDAs), biologics license applications (BLAs), and supplements who are planning to conduct clinical studies in neonatal populations. This guidance supplements the FDA draft guidance entitled *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014), as it addresses general clinical pharmacology considerations in neonates, a pediatric subpopulation.[2] The issuance of this draft guidance on clinical pharmacology considerations for neonatal studies for drugs and biological products is required under section 505(d)(2) of the FDA Reauthorization Act of 2017 (FDARA).[3]

This guidance addresses the clinical pharmacology considerations for any planned studies in neonates, whether the studies are conducted pursuant to section 505A of the Federal Food, Drug, and Cosmetic Act (FD&C Act),[4] section 505B of the FD&C Act,[5] or neither. This guidance does not discuss the timing to initiate neonatal studies. Questions regarding the appropriate

[1] This guidance has been prepared by the Neonatal Clinical Pharmacology Working Group in the Office of Clinical Pharmacology in the Center for Drug Evaluation and Research in collaboration with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] For purposes of this guidance, references to "drugs" and "drug and biological products" includes drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act or Act) (21 U.S.C. 355) and biological products licensed under 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) that are drugs.

[4] Section 505A of the FD&C Act is often referred to by the acronym of the Act that created it, the Best Pharmaceuticals for Children Act (BPCA).

[5] Section 505B of the FD&C Act is often referred to by the acronym of the Act that created it, the Pediatric Research Equity Act (PREA).

timing for the initiation of neonatal studies should be discussed with the relevant FDA review division.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In 2012, the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) were made permanent under Title V of the Food and Drug Administration Safety and Innovation Act (FDASIA).[6] FDASIA also requires that all BPCA requests for pediatric drug studies include a rationale for not including neonatal studies if none are requested.

Given that most drugs used in neonatal intensive care units (NICUs) are used in an off-label capacity, it is important that drug studies be conducted in neonates to address gaps in pediatric labeling information. In addition, therapies need to be developed for conditions unique to neonates. New approaches to the study of drugs in neonates should consider the diversity of the patient population and underlying conditions that are cared for in NICUs.

During in utero development, there are significant physiological changes in the fetus involving the normal expression and maturation of organs and tissues including enzyme systems, receptors, transporters, and neurotransmitters. Once fetal development is interrupted by preterm delivery, the normal developmental trajectory of these systems is altered based on the physiological changes that occur after birth. Postnatal development can also be adversely affected by concurrent illnesses, resulting in altered maturation of organs and tissues and affecting the systems responsible for product absorption (A), distribution (D), metabolism (M), and excretion (E) (ADME).

Gestational age (GA) at birth, postnatal age (PNA), and other factors (e.g. concurrent illness, underlying disease) can alter the pharmacokinetic (exposure) and pharmacodynamic (response) characteristics of a drug, which are essential components of the clinical pharmacology assessment. For example, a neonate born at 24 weeks gestation who is 4 weeks PNA is physiologically different compared to a 28-week gestation neonate who has just been born. The clinical pharmacology assessment should include a range of gestational ages, postnatal ages, and body weights, if feasible, unless the drug is intended to treat only a specific neonatal subpopulation.

Leveraging knowledge and data obtained from adult, preclinical, and other pediatric studies coupled with innovative quantitative approaches can help predict neonatal doses and optimal

[6] Title V Sec 501 (a) of FDASIA can be found at: https://www.congress.gov/112/plaws/publ144/PLAW-112publ144.pdf

clinical trial designs. Using quantitative approaches such as population pharmacokinetics (PopPK) and physiologically based pharmacokinetic (PBPK) modeling is critical to inform neonatal drug development.

Detailed planning of neonatal clinical pharmacology studies, including issues of feasibility, requires input from a multidisciplinary team involved in neonatal care, including parents. The submission of the initial pediatric study plan (iPSP)[7] is intended to encourage sponsors to consider pediatric studies early in product development, and when appropriate, begin planning for these studies. The PSP should include plans for neonatal studies unless a waiver for neonates is sought. If the PSP contains neonatal studies, the plan should include: (1) an outline of the neonatal study or studies that the applicant plans to conduct (including, to the extent practicable, study objectives and design, age groups (including neonatal subpopulations if relevant), relevant endpoints, and the statistical approach); (2) any request for a deferral or partial waiver if applicable, along with any supporting information; and (3) other information recommended in relevant FDA guidance.

III. DEFINITIONS AND SUBGROUP CLASSIFICATIONS

Historically, the neonatal period was defined as 28 days from delivery. The survival of preterm infants as premature as 22-23 weeks gestation at birth has complicated the use of this historical definition, as a 23-week gestation infant may require hospitalization in a NICU for 3 to 4 months because of complications from prematurity.

In this guidance, as in the International Council for Harmonisation (ICH) E11 addendum (18 August 2017)[8], the *neonatal period* is defined for the term and post-term newborn as the day of birth plus 27 days, and for the preterm newborn, as the day of birth, through the expected date of delivery plus 27 days. This definition is consistent with consideration of neonates as pediatric patients up to 44 completed weeks post-menstrual age (PMA). PMA has been used to date a gestation from the first day of the mother's known or reported last menstrual period and may be used either to define the GA at birth or the GA at birth plus the PNA. On the day of birth, PMA is equal to the GA.

Furthermore, the neonatal population could be categorized into subgroups based on a variety of factors. The following are examples of classifications:

Classification based on GA at birth:

- Preterm neonates at the border of viability: 22 to <24 weeks GA
- Extremely preterm neonate: 24 to <28 weeks GA

[7] See the FDA draft guidance for industry entitled *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (March 2016). When final, this guidance will represent the FDA's current thinking on this topic.

[8] The addendum to ICH E11 can be found at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm530012.pdf.

- Very preterm neonate: 28 to <32 weeks GA
- Moderate-to-late preterm neonate: 32 to <37 weeks GA
- Term neonate: 37 to <42 weeks GA
- Post-term neonate: ≥42 weeks GA at birth

Classification based on weight at birth:

- Preterm neonates at the border of viability: <600 grams
- Extremely low birth weight neonates (ELBW): <1000 grams
- Very low birth weight neonates (VLBW): <1500 grams
- Low birth weight neonates (LBW): <2500 grams

Other classifications:

- Small for gestational age (SGA) neonates: Birth weight less than the 10th percentile
- Large for gestational age (LGA) neonates: Birth weight greater than the 90th percentile

Depending on the needs of an individual drug development program, the classifications described above may be applicable for defining more homogeneous groups of neonates for inclusion in a trial or for stratifying neonatal populations enrolled in a trial.

When designing studies, it is important to consider stratifying the neonatal population to decrease heterogeneity. While neonates can be grouped by GA and/or weight at birth, PNA is another important variable to consider for stratification, as there are significant ADME changes related to PNA. For example, ADME characteristics may be very different for an extremely preterm infant in the first few hours of life, compared to the first few days after birth and compared to more than a week after birth. These characteristics also are different for an extremely preterm infant compared to a moderate-to-late preterm infant. All of these factors are important in the context of the biologic pathway of the drug being studied, as they may directly affect organ and tissue responsiveness and drug disposition. In addition, disparities at both ends of the growth spectrum (e.g. SGA, LGA) can impact developmental physiology and pharmacology. If patient stratification is based on birth weight, LGA infants may be assumed to be more mature than they actually are based solely on weight criteria.

IV. GENERAL CONSIDERATIONS

Before initiating neonatal clinical pharmacology studies, the sponsor should assess the available scientific information regarding the mechanism of action of the drug, the pharmacokinetics (PK) of the drug, and the ontogeny of any organs and tissues that are involved in the predicted response to the drug or its metabolites. This scientific information may be derived from several sources, including applicable animal models, in vitro studies, and other potentially relevant clinical studies. This information can be used to develop models and perform simulations to inform neonatal studies.

Model development requires an in-depth knowledge of the ontogeny of the target organs and tissues as well as the ontogeny of the organs and tissues involved in the ADME of the product and metabolites. The current gaps in this scientific information in neonates may limit the full potential of the application of modeling and simulation in this context. However, as this scientific information becomes available, these data can be incorporated into models to inform the design of neonatal studies.

Neonates may be uniquely susceptible to drugs that cross the blood-brain barrier and drugs that alter general physiologic parameters. Because of developmental and growth considerations, it may be necessary to follow neonates for potential safety issues longer than what is usually recommended for older children and adults. While long-term endpoints may be necessary to assess the safety and efficacy of drugs administered in the neonatal period, it is also important to develop short-term endpoints where feasible, given the challenges associated with long-term outcome studies. For all endpoints, it is important to consider the effects of sex, ethnicity, race, social, and environmental influences.

A. Pharmacokinetics

Adequate characterization of the PK of a drug can help to optimize dose selection for neonatal studies. In the neonatal population, inter- and intra-individual variability in pharmacokinetic measures are affected by multiple factors, for example, size, abnormalities in fetal growth, maturation (as delineated by PMA and PNA), underlying illnesses, and concomitant medications. Factors that may contribute to variability should be documented as part of the trial for later analysis. To account for this variability, it may be important to evaluate the product across a wide spectrum of PMA and PNA subgroups of neonates, if the indication to be studied is relevant in those populations.

1. Absorption

There are multiple developmental changes in neonates that can affect absorption. Many of these factors have unique ontogenic differences in the neonatal population which must be taken into consideration in any neonatal trial (e.g., gastric acidity, rates of gastric and intestinal emptying, surface area of the absorption site, gastrointestinal metabolizing enzyme systems, gastrointestinal permeability, biliary function, transporter expression, mode of administration, type of enteral feeding, and cutaneous maturation). Developmental changes in skin, muscle, and fat, including changes in water content and degree of vascularization, can affect absorption patterns of medicinal products delivered by intramuscular, subcutaneous, or percutaneous routes.

In general, when designing pharmacokinetic studies in neonates, consider that the absorption for products administered non-intravenously may be different in the neonatal population compared to older children.

2. Distribution

Distribution of a drug can be affected by changes in body composition, such as changes in total body water and adipose tissue, which are not necessarily proportional to changes in total body

weight. At birth, neonates have a higher total body water content, which is primarily extracellular. The proportion of total body water, as a percentage of body weight, increases with decreasing PMA. After birth, term neonates generally lose up to 10 to 15 percent of their total body water in the first postnatal week followed by a return to birth weight by 10 to 14 days PNA. For preterm infants the total body water loss may be greater than in term infants, and the recovery of birth weight may take longer. Blood flow to an organ or tissue (e.g. brain, liver) may differ between term and preterm infants, and differ from blood flow in older pediatric and adult populations. These differences may result in altered tissue distribution of the drug.

Plasma protein-binding and tissue-binding changes arising from changes in body composition with postnatal growth and development may also influence drug distribution. The concentrations of circulating proteins and the degree of protein binding of a drug may be lower in preterm and term infants compared to older children and adults. In addition, serum protein concentrations may remain low for weeks in the critically ill preterm infant. For drugs that are protein bound, preterm infants may have increased exposure to free, unbound concentrations of the drug which may impact its efficacy and safety. Additionally, for neonates, drugs that are bound to albumin may displace bilirubin.

When designing pharmacokinetic studies in neonates, consider the following when feasible:

- Characterize protein binding, particularly for drugs with high protein binding. For drugs that are highly protein bound, collect serum protein levels in neonates to evaluate the potential impact on PK (see section J. Application of Quantitative Approaches).
- Given the risk of hyperbilirubinemia in neonates, it may be important to assess the displacement of bilirubin from the albumin binding site if the drug is likely to bind to albumin.

3. Metabolism

Drug metabolism commonly occurs in the liver, but may also occur in the blood, gastrointestinal tract, kidney, lung, and skin. Information on the metabolism of specific drugs in neonates is generally limited. Each metabolic pathway has unique ontogenic characteristics that should be considered when designing clinical pharmacology studies in neonates. In addition, some metabolizing enzymes may have higher expression and activity in neonates compared to older populations (e.g., CYP3A7 and CYP3A4), respectively.[9,10]

Before conducting a clinical pharmacology study in neonates, consider the following:

[9] Lacroix D, M Sonnier, A Moncion, G Cheron, and T Cresteil, 1997, Expression of CYP3A in the Human Liver - Evidence that the Shift Between CYP3A7 and CYP3A4 Occurs Immediately After Birth, Eur J Biochem, 247(2):625-34.

[10] Fanni D, R Ambu, C Gerosa, S Nemolato, M Castagnola, P Van Eyken, G Faa, and V Fanos, 2014, Cytochrome P450 Genetic Polymorphism in Neonatal Drug Metabolism: Role and Practical Consequences Towards a New Culture in Neonatology, Int J Immunopathol Pharmacol, 27(1):5-13.

- To plan neonatal pharmacokinetic studies. a thorough review of the scientific literature should be conducted to obtain information about the metabolic pathways for the specific drug.

- As the postnatal ontogeny of many of these metabolic pathways has not been fully elucidated, it may be necessary to perform additional in vitro or preclinical studies.

- When appropriate, microdosing studies in neonates may be conducted to assess for potential ontogenic differences in the metabolic pathway compared to older populations.[11, 12]

4. Excretion

Drug excretion by the kidneys is the net result of glomerular filtration, tubular secretion, and tubular reabsorption. The glomerular filtration rate (GFR) is low in neonates, particularly in those born before 32 weeks PMA and increases rapidly after birth.[13, 14, 15] For drugs that are primarily renally excreted, both PMA and PNA may have a significant effect on the systemic exposure of a drug.[16] Pulmonary and gastrointestinal/biliary routes of excretion may also be important for certain drugs and may be affected by the ontogeny of those organ systems.

Before conducting a clinical pharmacology study in neonates, consider the following:

- The ontogeny of transport systems, particularly those involved in active transport, have not been well elucidated in neonates. Ontogenic differences in transport systems may have an impact on neonatal PK.

[11] Roth-Cline M and RM Nelson, 2015, Microdosing Studies in Children: A US Regulatory Perspective, Clin Pharmacol Ther, 98(3):232-3.

[12] Mooij MG, E van Duijn, CAJ Knibbe, K Allegaert, AD Windhorst, J van Rosmalen, NH Hendrikse, D Tibboel, WHJ Vaes, and SN de Wildt, 2017, Successful Use of [^{14}C]Paracetamol Microdosing to Elucidate Developmental Changes in Drug Metabolism, Clin Pharmacokinet, 56(10):1185-1195.

[13] Anderson BJ and NHG Holford, 2008, Mechanism-Based Concepts of Size and Maturity in Pharmacokinetics, Annu Rev Pharmacol Toxicol, 48:303-32.

[14] Rhodin, MM, BJ Anderson, AM Peters, MG Coulthard, B Wilkins, M Cole, E Chatelut, A Grubb, GJ Veal, MJ Keir, and NHG Holford, 2009, Human Renal Function Maturation: A Quantitative Description Using Weight and Postmenstrual Age, Pediatr Nephrol, 24:67-76.

[15] Mahmood I and MA Tegenge, 2019, A Comparative Study Between Allometric Scaling and Physiologically Based Pharmacokinetic Modeling for the Prediction of Drug Clearance From Neonates to Adolescents, Pediatr Pharmacol, 59(2):189-197.

[16] Wang J, SS Kumar, CM Sherwin, R Ward, G Baer, GJ Burckart, Y Wang, and LP Yao, 2018, Renal Clearance in Newborns and Infants: Predictive Performance of Population-Based Modeling for Drug Development, Clin Pharmacol Ther, doi:10.1002/cpt1332, epub ahead of print.

- For drugs that are known substrates of transporters, information gained from the conduct of pharmacokinetic studies in neonates may help elucidate the ontogenic trajectory of the transporter of interest.

5. Clearance

Plasma clearance can be defined as the volume of plasma which is completely cleared of drug in a given time period. Clearance as a function of age (PMA and PNA) is generally a valuable parameter for determining the dose for each neonatal subgroup and may change rapidly based on the PNA.

- Clearance from target organs and tissues may also differ between neonates and older children and adults; therefore, compartment sampling (e.g. cerebrospinal fluid), when feasible, may be useful to determine the optimal dosing.

- As the clearance of a drug may be substantially different in various neonatal subgroups based on both PMA and PNA, it may be necessary to assess the clearance of a drug in each subgroup being studied.

6. Additional Factors

As increasing scientific data are garnered related to the prenatal and postnatal ontogeny of organs and tissues for ADME parameters in each of the neonatal subgroups, this information could be used to generate PBPK models to help design subsequent dosing strategies in those subgroups.[17]

B. Pharmacodynamics

Sponsors should collect and analyze both pharmacokinetic and whenever possible, pharmacodynamic data in neonatal studies to determine how the two are linked with respect to exposure-response (E-R). Pharmacodynamics (PD) may include the effect of the drug on biomarkers or clinical endpoints for both safety and efficacy. These measurements may help to determine if the E-R relationship of the drug in neonates is similar to that observed in older children and adults. If the clinical endpoints cannot be measured directly, then an appropriate biomarker to substitute for the clinical efficacy or toxicity endpoint should be selected. As drugs given to neonates may affect multiple organ systems, it may be necessary to evaluate several biomarkers. In neonates, the ontogeny of the tissues and organs that are targeted by the drug may be critically important in predicting the potential degree of response, thus altering the E-R relationships. These data are integral to any consideration of extrapolating efficacy data from studies in older children and adults.

Before conducting a clinical pharmacology study in neonates, consider the following, when feasible:

[17] See the FDA guidance for industry entitled *Physiologically Based Pharmacokinetic Analyses — Format and Content* (September 2018).

- All prior information on E-R relationships of the drug in adults and pediatrics can help inform the neonatal studies.

- A poor or incomplete understanding of the natural history and pathophysiologic mechanisms of many neonatal conditions hinders the identification of clinically relevant pharmacodynamic biomarkers. Sponsors should initiate discussions early with the FDA when considering the use of novel biomarkers of response in neonatal studies.

C. Pharmacogenomics

Genetic differences that affect both the exposure of and response to a drug are increasingly documented, but the relationship between genomic profiles and developmentally regulated gene expression has not been extensively studied in the neonatal population. Therefore, consider the following, if feasible:

- If there are pharmacogenetic differences that affect the PK, efficacy, and safety of a drug in older children and adults, pharmacogenetic analysis is recommended in neonates.

V. STUDY DESIGN CONSIDERATIONS

Conventional pharmacokinetic studies that include intensive blood sampling can rarely be undertaken in neonates because of their limited circulating blood volume. Another consideration is the variability in the study population (e.g., a population undergoing rapid and varying rates of maturation) which makes collection of clinical pharmacology information (e.g. PK, PD, etc.) uniquely challenging. Hence, it is important to use all available information and innovative approaches when designing a neonatal study. When designing neonatal clinical studies, sponsors should be mindful that modeling and simulation and pharmacologic considerations are often critical for the successful completion of a study. Some approaches that can inform the design and dose selection of neonatal studies include PopPK, PBPK modeling, and/or pharmacokinetic/pharmacodynamic modeling approaches.[18] However, relevant ontogenic data with respect to ADME should be available before robust and accurate models can be developed for use in neonatal clinical studies.

The following sections describe considerations for specific trial design elements when developing a neonatal study plan.

A. General Approaches to Providing Substantial Evidence of Safety and Effectiveness in Neonates

[18] See the following FDA guidances for industry: (1) 2018 *Physiologically Based Pharmacokinetic Analyses — Format and Content*, (2) *Population Pharmacokinetics* (February 1999), and (3) *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* (April 2003).

There are several approaches to providing substantial evidence of safety and effectiveness for drugs for the pediatric population:[19]

- Considering the distinct disease processes seen in the neonatal population, it is expected that pediatric extrapolation of effectiveness from other populations (e.g. adults, older children) would be infrequently used. Regardless of the approach used to provide evidence of effectiveness, safety data should be obtained for all drugs studied in neonates. The magnitude of the safety database needed is determined by several factors, including for example, experience with similar drugs in populations of older children, adults, and neonates and the seriousness of the adverse reactions in the adult or pediatric populations.

- Most drugs developed for use in neonates require adequate and well-controlled studies for the specific neonatal indication. The prospect of a direct benefit to the neonatal study participants would depend on the disease or condition and its severity, the availability of alternative treatments, and the absence of a major or significant safety concern based on data in adults, older children, or animal and in vitro models (if no human data are available) (see Section V.K). The analysis of all the available scientific information may allow for concurrent drug development in the neonatal population.

B. Study Population

When conducting clinical pharmacology studies in neonates, the population enrolled should involve neonates that have the disease or condition of interest or, in some cases, neonates who may be at risk for the disease or condition of interest.

To account for variability in age, it may be necessary to evaluate the product across a wide spectrum of PMA and PNA subgroups of neonates, as long as the indication to be studied is relevant in those subgroups (see Neonatal Definition and Subgroup Classifications). It may be necessary, when including a wide spectrum of neonates, to plan for subgroup analyses (see Data Analysis).

C. Dose Selection

Selection of an appropriate dose range to be studied is critical in deriving rational dosing recommendations for the neonatal population. Investigators should use all existing pharmacokinetic and pharmacodynamic data (from adults, older pediatric patients, etc.) to help determine an initial dose in neonates. Clinical trial simulations that integrate PK, PD, biomarkers, and disease progression may help make this initial determination. In addition to the factors outlined in the 2014 FDA draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*, dose selection in neonates should also consider the PMA and PNA.

[19] For a more complete discussion on providing evidence of efficacy and safety in pediatric patients, see the 2014 FDA draft guidance for industry entitled *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*.

The rapid changes in growth and development occurring in neonates may require dosing adjustments over short periods of time (e.g. in certain instances the initial dosing of anti-infective agents changes after 24 hours). Depending on the range of PNAs and PMAs being studied and the duration of intended treatment, dosing regimens could become even more complex. Often, significant uncertainty about the dose in neonates necessitates alternative approaches that may involve titration of the dose, adaptive trial designs, or the use of therapeutic drug monitoring (TDM) during the trial. TDM may be particularly useful when there is known drug toxicity, or higher exposures are expected in neonates.

Given the unique ADME characteristics in neonates, different dosing regimens may need to be studied to optimize the exposure in various neonatal subpopulations. Occasionally, neonates may even require higher drug exposures than those needed in older children and adults to achieve adequate treatment effect; as a result, additional safety data are needed to support the use of higher doses in neonates.

Given the uniqueness of some neonatal conditions, it is possible that in certain circumstances first-in-human studies may need to be conducted in the neonatal population. In a first-in-human scenario (e.g. the target population is the neonatal population only), where sufficient data from adults or older children are lacking, sponsors should initiate discussions early with the FDA to determine potential approaches to dose selection.

D. Formulation

Proposed trials in the neonatal population require an age-appropriate dosage formulation. Approaches to developing these formulations, including preparation by a pharmacist in a licensed pharmacy, are detailed in the 2014 FDA draft guidance entitled *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*.[20] Neonates may present unique challenges associated with formulations and dosing. All aspects of the formulation, including the salt forms of the active ingredient, the excipients, and the volume of the unit dose, should be considered. Formulations should be developed to permit accurate dosing, especially given the potentially small unit doses. Studies of drugs in neonates should account for potential interactions with tubing used for both parenteral and enteral administration and any potential interactions with co-administered fluids (including parenteral nutrition), enteral nutrition, and other therapeutic products.

The route of administration is important in neonates, given that many neonates may be critically ill and unable to receive enteral products. While most products are developed for parenteral administration, other routes (e.g. enteral, inhalational, intraocular, transcutaneous, intramuscular, subcutaneous or rectal) can be considered when appropriate, depending on the condition to be treated and the clinical status of the neonate. The bioavailability of any non-parenteral formulation used in neonatal studies should be characterized in relation to the formulation used in older children and adults. Typically, bioavailability studies of age-appropriate formulations are conducted in adults; however, the potential for developmental differences in absorption between neonates and adults should be considered.

[20] When final, this guidance will represent the FDA's current thinking on this topic.

Considerations for excipients are particularly important in the neonatal population given that the accumulation of excipients may be significantly higher in neonates due to immature organ function. In general, the sponsor should minimize the use of excipients in neonatal formulations whenever possible. Excipients with known toxicity in neonates should not be used (e.g. ethanol, propylene glycol, benzyl alcohol).

E. Sample Size

Investigators should consider the necessary number of neonates in various subpopulations to establish accurate dosing. Justification should be provided for the sample size selected. The precision of pharmacokinetic and pharmacodynamic parameters in the sample size calculation is critical for neonatal studies.[21] For example, one approach is to prospectively target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for the drug in each pediatric stratum with at least 80% power.[22] Prior knowledge of the disease, drug exposure, and pharmacodynamic response from older children and adult data can be used to estimate the sample size for neonatal studies. The sponsor should account for sources of variability, including inter- and intra-subject variability, differences between neonatal subgroups, and differences between neonates and older children and adults in the final selection of the sample size for each neonatal subgroup.

Given the challenges associated with conducting studies in neonates, alternative and innovative approaches to traditional sample size requirements may be suitable if they improve the interpretability of trial results. Clinical trial simulations that integrate pharmacokinetic and pharmacodynamic aspects may help to design trials with feasible sample sizes. Practical considerations should be taken into account when determining the sample size if it is not possible to recruit adequate numbers of participants to achieve the desired precision of parameter estimates. The sample sizes needed for studies of a drug product in neonatal subgroups should be discussed with the Agency prior to conducting the study.

F. Sampling

More often than not, blood samples are the primary samples collected in neonatal studies. Other types of samples, such as CSF, urine, or saliva can be informative but are not as readily collected for the characterization of PK and PD.

1. Considerations for Blood Sample Volume Limits

Blood sample volumes needed for research studies should be limited to the least possible volume required for testing to minimize risk to the patient. The sponsor should account for blood drawn

[21] See the 2014 FDA draft guidance for industry entitled *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*.

[22] See the 2014 FDA draft guidance for industry entitled *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*.

for the study in addition to blood drawn for routine clinical assessments. If possible, blood needed for research studies should be timed with clinically indicated blood draws to minimize the blood volume and decrease the number of needle sticks or draws from an indwelling catheter.[23,24] In some situations, blood from scavenged samples (i.e., samples obtained from surplus blood drawn during of clinical care) could improve the feasibility of such studies.

Greater consideration may be needed in infants where illnesses specifically impact the ability to replace hemoglobin. It is important to know how slowly red cells will be replenished in the sick neonate (which reflects GA, PNA, and severity and type of illness) when determining the number of samples and sample volumes for the purposes of the study. In general, neonatal blood volumes are approximately 85 mL/kg, increasing to 105 mL/kg by the end of the first month.[25,26,27] Studies have looked at the association between blood draws and the need for transfusion. In the first study, approximately 13 percent of the total blood volume (TBV) was removed and 19 percent of these patients required transfusion.[28] In a second study, approximately 18 percent of the TBV was withdrawn, and 53 percent of the patients required transfusion.[29] In a third study, patients had 4.5 percent of the TBV drawn, resulting in a decrease in hemoglobin of 3.4 g/dL.[30]

Several academic centers and institutional review boards (IRBs) have published their guidelines for total blood volume limits for neonatal studies (including blood draws for both research and clinical care purposes). In general, these ranges vary between 1 to 5 percent of the TBV for a single draw or over a 24-hour period and 3 to 10 percent of the TBV over a month. The sponsor should consider the amount of blood drawn for clinical purposes and the clinical status of the patient. In addition, a minimum hemoglobin should be set before a research blood draw. Literature on minimum hemoglobin values in neonatal patients is limited; however, one

[23] Howe SRC, 2011, Blood Sample Volumes in Child Health Research: Review of Safe Limits, Bulletin of the World Health Organization, 89:45-53.

[24] Veal GJ, 2014, Blood Volumes in Pediatric Clinical Trials: A Review of Current Regulations and Guidance for Research Studies, Clin. Invest, 4:1005-1011.

[25] Guidelines for Blood Volumes in Clinical Trials (Especially in Pediatric Clinical Trials): http://onbiostatistics.blogspot.com/2011/02/guidelines-for-blood-volumes-in.html

[26] Howe SRC, 2011, Blood Sample Volumes in Child Health Research: Review of Safe Limits, Bulletin of the World Health Organization, 89:45-53.

[27] Pearson H, 2003, Blood and Blood Forming Tissues, Rudolph's Pediatrics, 21st ed, New York:McGraw-Hill, 1521.

[28] Madsen LP, MK Rasmussen, LL Bjerregaard, SB Nøhr, and F Ebbesen, 2000, Impact of Blood Sampling in Very Preterm Infants, Scand J Clin Lab Invest, 60:125-32.

[29] Hack KE, CM Khodabux, JS von Lindern, HA Brouwers, SA Scherjon, HJ van Rijn, JA van Hilten, A Brand, and GC Page-Christiaens, 2008, Need for Blood Transfusion in Premature Infants in 2 Dutch Perinatology Centres Particularly Determined by Blood Sampling for Diagnosis, Ned Tijdschr Geneeskd, 152:1419-25.

[30] Testa M, F Birocchi, P Carta, and V Fanos, 2006, Causes of Anaemia in Very Low Birth Weight Infants: Phlebotomy Losses are not the First Accused, Minerva Pediatr, 58:263-7.

institution set this minimum at 7.0 g/dL for a stable neonate and 9.0-10 for a neonate with respiratory or cardiovascular compromise. These values would be dependent on the PMA and PNA of the neonates in the study.

When planning a neonatal pharmacokinetic and/or pharmacodynamic study, sponsors should justify their proposed sampling scheme and the number of samples to be collected per patient.

2. Sampling Schemes

Given the blood volume considerations for neonates, sparse sampling is a practical approach for obtaining pharmacokinetic data in neonatal studies. To effectively inform sparse sampling in neonates, it is essential to leverage what is known about the ontogeny of relevant organ and enzyme systems as well as pharmacokinetic information that may be available in adults or older children. The sampling scheme should allow for the characterization of the clinically relevant exposure metrics that inform dosing. Practical considerations should also be taken into account when determining a feasible sampling scheme.

Opportunistic sampling (i.e., sampling around the time of clinically indicated blood draws) and the use of scavenged samples may be used for pharmacokinetic sampling and characterization. Opportunistic designs and scavenged sampling may increase the feasibility of conducting neonatal PK studies. Parents may be more willing to enroll their child in such a study given that additional blood draws beyond those of the standard-of-care may not be required.

When using opportunistic or scavenged samples, it is important to ensure sample stability, given that these samples are not generally collected with the primary intention of characterizing PK, and the approach to their collection and handling may differ from traditional pharmacokinetic samples. Careful planning is required when using an opportunistic approach and scavenged sampling, as there is less control of the sampling time with respect to the dosing time of the drug of interest and other concomitant medications. Lack of planning could increase the possibility that pharmacokinetic samples over critical periods of the dosing interval will not be collected and may render the information obtained unreliable.

The sponsor should assess the correlation between scavenged sample concentrations and prospectively collected pharmacokinetic sample concentrations to understand the extent to which drug concentration measurements are affected.[31] The acceptability of this approach depends on the quality and quantity of samples, the number of subjects, the total number of samples, and the variability of the data.

Because of the above considerations, it is important to prospectively plan when using opportunistic or scavenged samples. The protocol should specify a standardized collection scheme, storage and handling conditions, accurate recording of the sampling times, the dose, and the dosing time of the drug of interest as well as any concomitant medications. When planning to employ such approaches, sponsors should seek advice from the FDA.

[31] Autmizguine J, DK Benjamin Jr, PB Smith PB, M Sampson, P Ovetchkine, M Cohen-Wolkowiez, and KM Watt, 2014, Pharmacokinetic Studies in Infants Using Minimal-Risk Study Designs, Curr Clin Pharmacol, 9(4):350-358.

3. Sample Acquisition Methods

Sampling technique is critical when using an available neonatal indwelling intravenous or intra-arterial catheter. Any sampling plan should also take into consideration the use of umbilical catheters and small caliber vascular access devices. If possible, pharmacokinetic samples should be obtained from a separate site other than that used for the administration of the drug product. While it is ideal to collect blood samples for analysis from the circulating blood volume, heel sticks can be used in the neonatal population if the data quality is unaffected. Regardless of the route of access, it is important to distinguish between arterial and venous samples unless there are data to suggest that there is no difference in drug concentrations between them.

When possible, opportunistic sampling or scavenging of biological fluids that are already being collected as part of routine clinical care such as cerebrospinal fluid or bronchial fluid, may provide additional pharmacokinetic information. For example, cerebrospinal fluid collected for clinical purposes may add to the understanding of the PK of the drug. However, proper collection and storage of the sample as well as recording the time the sample was collected relative to the administration of the drug are critical to obtaining interpretable data.

While urine and saliva collection are non-invasive, the interpretation of data from such samples is also complicated and requires careful consideration before collecting. Non-invasive sampling using fluids may be useful if correlated with outcomes or blood or plasma drug levels. The volume of these samples in neonates may be small, and validation of the analysis in these small volumes should be provided.

From a feasibility perspective, recent literature reports suggest that dried matrix spots represent a potential methodology for acquiring biological samples. Dried matrix samples consist of a collection of biological fluid on blotting paper and typically require low volumes. There are several dried matrix spot methods which can include dried blood spots (DBS), dried urine spots (DUS) and dried plasma spots (DPS). The most common dried matrix spot used in the neonatal population is DBS. Its minimally invasive sampling technique, the low blood volume required, and the ease of sample storage and handling are potential advantages of DBS. When using such an approach, bioanalytical validation should be conducted. (see Bioanalytical Methods). If considering using such an approach, sponsors should initiate discussions with the FDA.

G. Bioanalytical Methods

An accurate, precise, sensitive, specific, and reproducible analytical method to quantify the parent drug and metabolites in the biologic fluids of interest is essential. Given the small sample volumes from neonates, micro-analytic techniques (e.g. ultra-low blood volume drug assays) should be considered. These techniques should be validated so that these methods can be used with confidence in neonatal studies.[32]

[32] See the FDA guidance for industry entitled *Bioanalytical Method Validation* (May 2018).

589 Characterization of the stability of scavenged samples is particularly essential, especially for
590 samples that may not be processed for long periods of time. The stability of the analyte in a
591 specific matrix and container system cannot be extrapolated to other matrices or container
592 systems. Bioanalytical testing of the collected samples should occur in a laboratory setting that
593 is conducive to the established processing requirements.
594
595 Some considerations for the bioanalyses of dried matrix spots include: the required hematocrit
596 (for DBS), the need for validated methods, the stability of the drug, the variability of the method,
597 and the homogeneity of the blood spot.[33, 34, 35] However, standardized sample acquisition
598 collection, proper testing techniques, and validated methods can reduce the number of limitations
599 associated with the biomatrix.
600
601 Sponsors are advised to obtain feedback from the FDA Office of Clinical Pharmacology early in
602 the neonatal drug development process to determine the appropriate bioanalytical methods for
603 each drug.
604
605 **H. Data Analysis**
606
607 The 2014 FDA draft guidance for industry entitled *General Clinical Pharmacology*
608 *Considerations for Pediatric Studies for Drugs and Biological Products* describes the two basic
609 approaches for performing pharmacokinetic analyses in pediatric patients: (1) a standard non-
610 compartmental pharmacokinetic approach and (2) a PopPK approach. The PopPK approach is
611 more feasible in the neonatal population as it minimizes the total volume of blood sampled per
612 individual. PopPK approaches leverage prior information obtained from studies in adults and
613 older children in conjunction with data collected from neonatal studies to provide estimates of
614 the drug's pharmacokinetic parameters and their associated variability. However, any models
615 that are developed for use in neonates should take into consideration all the ADME factors for
616 each PMA and PNA subgroup and be supported by additional scientific data.[36, 37, 38]
617

[33] Autmizguine, J, DK Benjamin, Jr, PB Smith, M Sampson, P Ovetchkine, M Coehn-Wolkowiez, and KM Watt, 2014, Pharmacokinetic Studies in Infants Using Minimal-Risk Study Designs, Curr Clin Pharmacol, 9(4):350-8.

[34] Liu, G, QC Ji, M Jemal, AA Tymiak, and ME Arnold, 2011, Approach to Evaluating Dried Blood Spot Sample Stability During Drying Process and Discovery of a Treated Card to Maintain Analyte Stability by Rapid On-Card pH Modification, Anal Chem, 83(23):9033-8.

[35] Blessborn, D, K Sköld, D Zeeberg, K Kaewkhao, O Sköld, and M Ahnoff, 2013, Heat Stabilization of Blood Spot Samples for Determination of Metabolically Unstable Drug Compounds, Bioanalysis, 5(1):31-9.

[36] International Neonatal Consortium: Second Annual Neonatal Scientific Workshop, March 7, 2016; Available from: https://c-path.org/programs/inc/.

[37] Kern, SE, 2009, Challenges in Conducting Clinical Trials in Children: Approaches for Improving Performance, Expert Rev Clin Pharmacol, 2(6):609-17.

[38] Rodieux, F, M Wilbaux, JN van den Anker, and M Pfister, 2015, Effect of Kidney Function on Drug Kinetics and Dosing in Neonates, Infants, and Children. Clin Pharmacokinet, 4(12):1183-204.

1. Application of Quantitative Approaches

The application of modeling and simulation (M&S) as a tool for dose selection in neonates is particularly challenging. The considerable variability in neonatal subgroups driven by differences in growth and maturation influences the outcomes of all types of models. In the absence of conducting a clinical trial in a large, diverse cohort of neonates, M&S can provide insights into dosing if such models are well formulated and executed. First, internal and external evaluations of the model should be performed to ensure that estimates of the drug's pharmacokinetic parameters are adequate and precise. Then, the model can be used to simulate dosing scenarios in the population for which the model was developed. Any trial design as a product of M&S should be flexible enough to mitigate the uncertainties inherent in the model outcomes. For example, in the commonly used sequential or staged study design, younger and younger cohorts are studied sequentially so that the trajectory of the dose-exposure or E-R relationships can be assessed. This conservative approach is widely used but may also significantly delay drug development in neonates, who are the youngest and most vulnerable age group. Alternative study designs coupled with M&S may offer neonatal drug development a more streamlined path forward.

2. Population Pharmacokinetics

The PopPK approach, described in the 1999 FDA guidance entitled *Population Pharmacokinetics* has been the most commonly used approach in neonatal drug development studies. PopPK uses non-linear mixed-effect modeling and allows for the analyses of sparse (limited number of blood samples per individual) and unbalanced data (unequal distribution of blood samples in various parts of the concentration-time profile in the individuals). These factors are particularly important as both scenarios are typically present in neonatal studies.[39,40]

3. Physiologically Based Pharmacokinetics

Another quantitative approach is PBPK modeling, a mechanistic modeling approach that incorporates the understanding of physiology and compound-specific information to predict the dose-exposure relationship.[41,42] While PBPK prediction incorporates a more mechanistic understanding, its application in neonates is particularly challenging due to the limited understanding of rapid changes in neonatal physiology and the maturation of ADME processes in this population.

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[39] Wang J, AN Edginton, D Avant, and GJ Burckart, 2015, Predicting Neonatal Pharmacokinetics from Prior Data Using Population Pharmacokinetic Modeling, J Clin Pharmacol, 55(10):1175-83.

[40] Ku, LC and PB Smith, 2015, Dosing in Neonates: Special Considerations in Physiology and Trial Design, Pediatr Res, 77(1-1):2-9.

[41] See the 2018 FDA guidance for industry entitled *Physiologically Based Pharmacokinetic Analyses — Format and Content*

[42] Maharaj, AR and AN Edginton, 2014, Physiologically Based Pharmacokinetic Modeling and Simulation in Pediatric Drug Development, CPT Pharmacometrics Syst Pharmacol, 3(11):1-13.

653
654 *4. Covariates and Phenotype Data*
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656 The following covariates for each neonate should be considered as part of data analysis: GA,
657 birth weight, birth length, birth head circumference, PMA, PNA, current weight, body surface
658 area (BSA), race or ethnicity, sex, diagnoses, concomitant and recent medications or intravenous
659 fluids (including blood transfusions), type and amount of enteral feedings, and relevant
660 laboratory tests that reflect the function of the organs responsible for drug metabolism and drug
661 excretion. The sponsor should examine the relationships between the covariates and the PK of
662 the drug of interest to assess the potential contribution of the covariates to the variability of
663 pharmacokinetic parameters. Having enough subjects with or without the covariates of interest
664 is important to determine the impact of these factors on the drug's PK. Also, the impact of
665 pharmacogenetic factors could be critical to data analysis in some instances; therefore, sponsors
666 are encouraged to collect DNA samples in neonatal pharmacokinetic studies, when feasible.
667
668 A quantitative model may incorporate covariates such that the importance of patient
669 characteristics (e.g. body size, PNA or PMA) or extrinsic factors (e.g. presence of concomitant
670 medication) on pharmacokinetic parameters is reflected, resulting in more precise estimates of
671 the PK of the drug on the next patient cohort.[43]
672
673 **I. Clinical Study Report**
674
675 The 2014 FDA draft guidance entitled *General Clinical Pharmacology Considerations for*
676 *Pediatric Studies for Drugs and Biological Products* describes the requirements for the Clinical
677 Study Report for neonatal studies. It is important to capture safety data in all clinical
678 pharmacology studies of neonates. Classification of adverse events in neonates may be difficult
679 given concomitant illnesses and medications. Any potential adverse events related to drug
680 administration should be documented.
681
682 **J. Data Submission**
683
684 The preferred submission standard for clinical data from neonatal studies is described in the 2014
685 FDA draft guidance entitled *General Clinical Pharmacology Considerations for Pediatric*
686 *Studies for Drugs and Biological Products*.
687
688 **K. Ethics**
689
690 Ethical considerations for pediatric studies are covered in the FDA draft guidance *General*
691 *Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products*.
692 It is recommended that an IRB have specific expertise in neonatal trials; furthermore, an
693 independent Data and Safety Monitoring Board (DSMB) may be necessary to oversee the trials,
694 and in such cases, should also have expertise with neonatal patients (see Section V.A).

[43] Wang J, AN Edginton, and G Burckart, 2015, Using Modeling and Simulation for Neonatal Drug Development, NeoReviews, 16(11):e648-52.