A Pediatric Research Imperative: Addressing Neonates in Drug Development

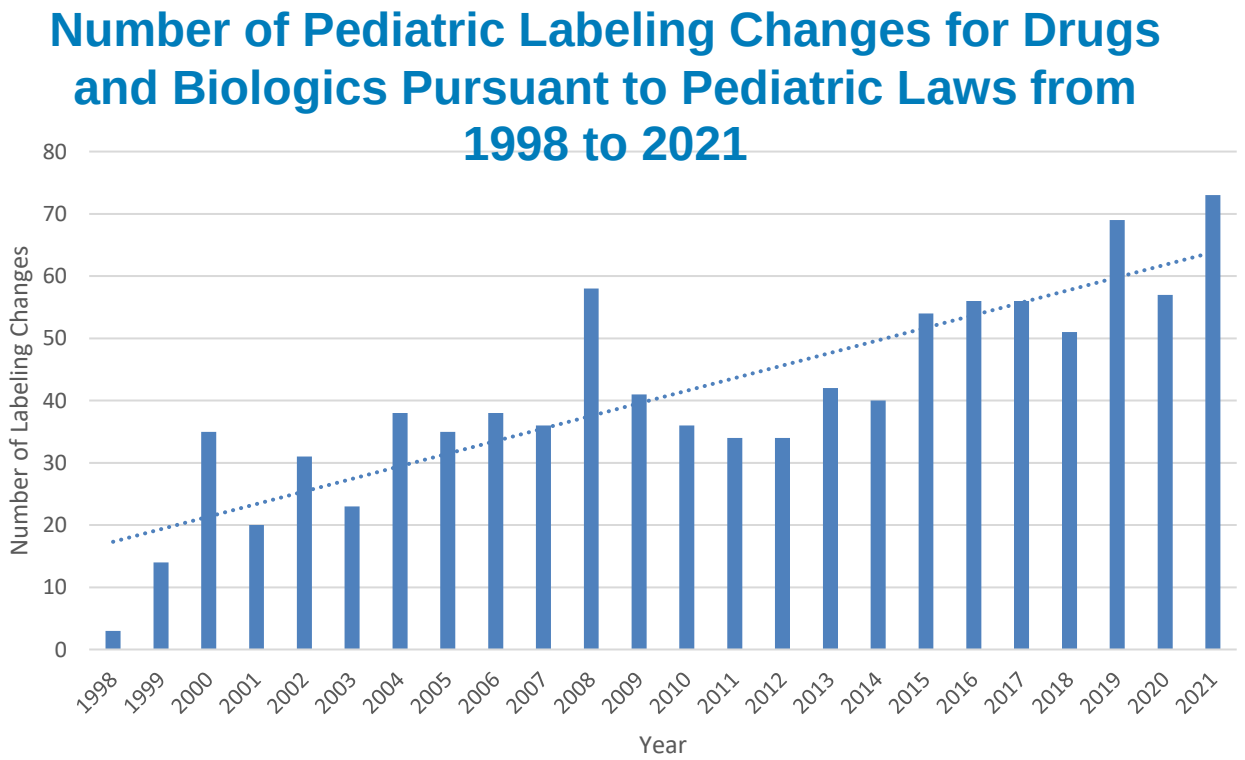
Dionna Green, MD, FCP
Director, Office of Pediatric Therapeutics
Office of Clinical Policy and Programs
OC | US FDA

Overview: Clinical Pharmacology Considerations for Neonatal Studies – February 15, 2023

Learning Objectives

- Describe how neonatal subpopulations can be defined for the purposes of study design and reporting
- Discuss clinical pharmacology considerations for clinical studies in neonates for drug development
- Discuss innovative approaches that can be incorporated into study design to address unique challenges in conducting neonatal studies

Pediatric Labeling Changes



Pediatric Labeling Changes Milestone

AAP News

Historic milestone: 1,000 drugs, biologics have new pediatric use information in labeling

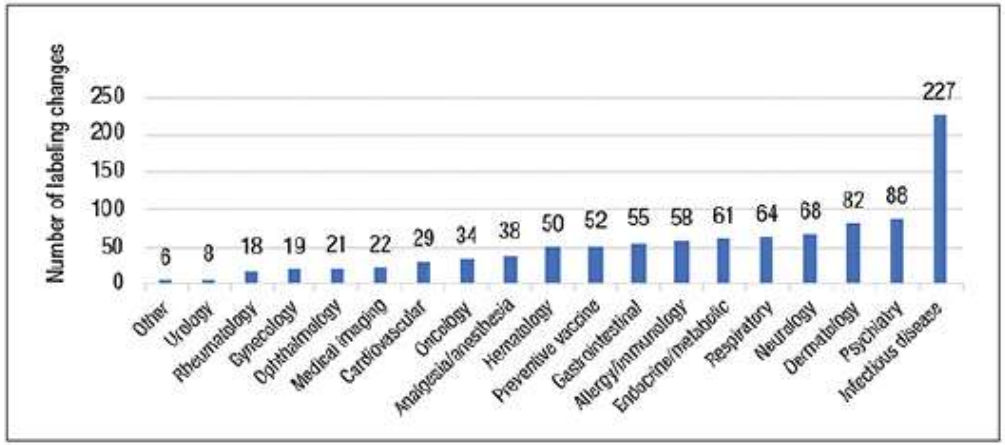
September 1, 2022

from the Food and Drug Administration

Article type: FDA Update

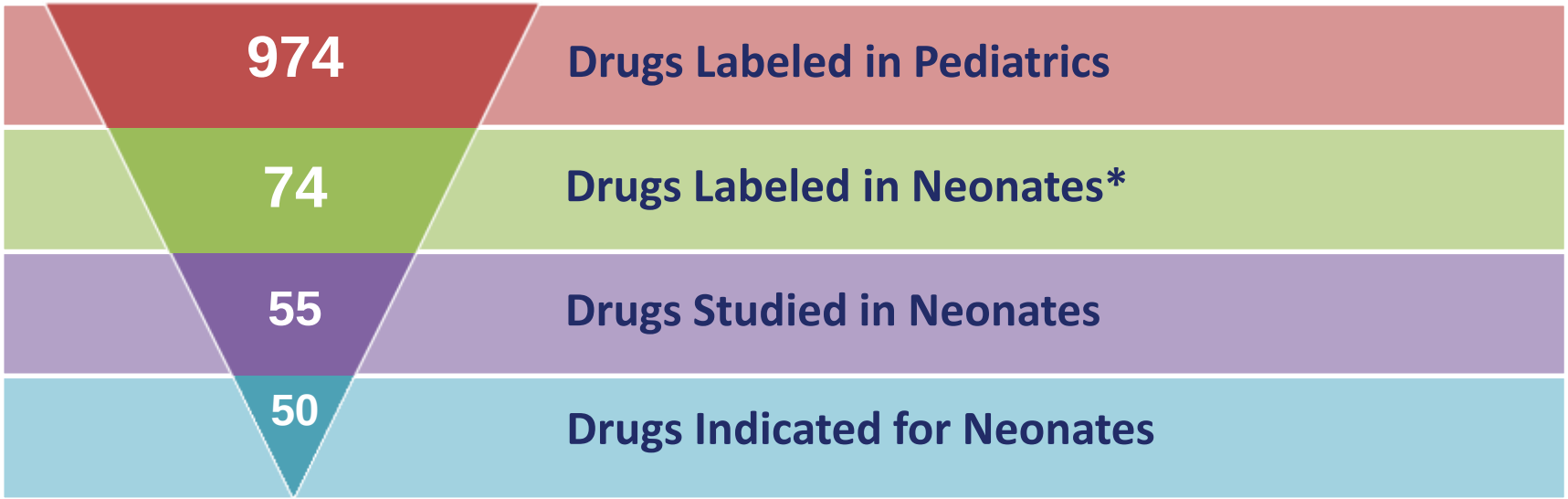
Topics: Pharmacology, Therapeutics

Figure 2. First 1,000 pediatric labeling changes pursuant to PREA, BPCA and the Pediatric Rule by therapeutic area



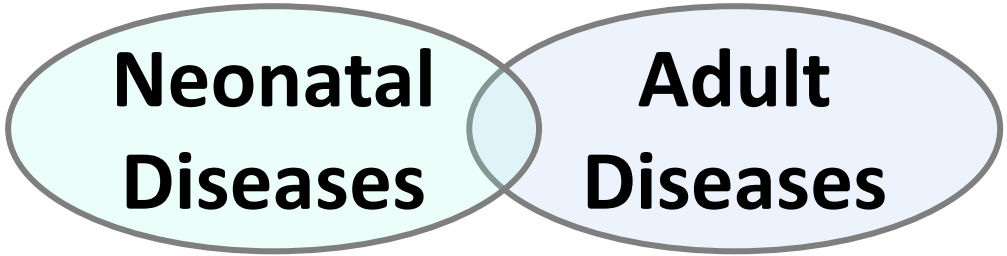
Labeling Changes for Neonates

Labeling Changes for Neonates Pursuant to BPCA and PREA through 2021



* 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.

Conditions Unique to the Neonate



- Extrapolation of efficacy from adult populations may be limited
- Critical to understand the natural history of the disease/condition
- Critical to identify biomarkers and appropriate measures of response

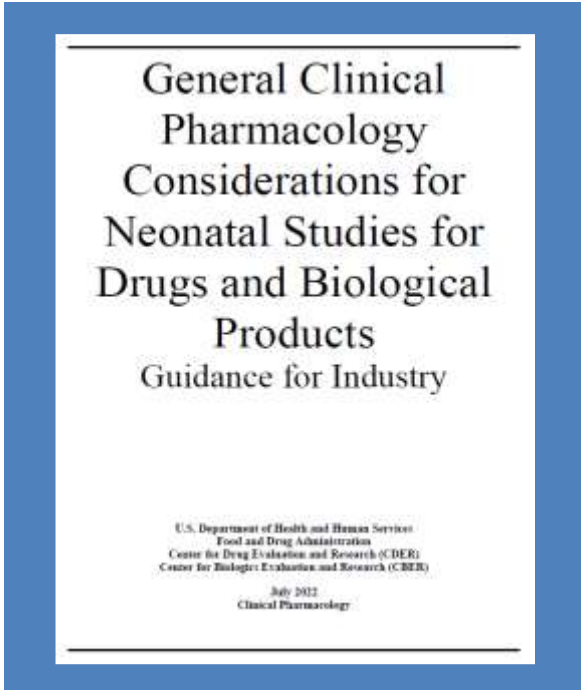
  - Respiratory distress syndrome
  - Intraventricular hemorrhage
  - Retinopathy of prematurity
  - Necrotizing enterocolitis
  - Persistent pulmonary HTN of the newborn
  - Hypoxic ischemic encephalopathy
  - Patent ductus arteriosus

FDASIA and Neonates

- FDA Safety and Innovation Act of 2012
  - Made permanent the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA)
  - Requires early planning of pediatric studies
- Emphasized the need for increased neonatal studies
  - Requires all Written Requests for pediatric studies to include a rationale for not including neonatal studies if none are requested
  - Required FDA to increase the number of personnel with expertise in neonatology; including on the Pediatric Review Committee (PeRC)
  - Requires FDA to report to the U.S. Congress every 5 years on efforts to increase the numbers of neonatal studies

FDARA and Neonates

- FDA Reauthorization Act of 2017
  - Made permanent the requirement for FDA to have personnel with expertise in neonatology
  - Required FDA to issue draft guidance on clinical pharmacology considerations for neonatal drug studies



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

Clinical Considerations for Neonatal Drug Development

An N. Massaro, M.D.
Supervisory Medical Officer
Office of Pediatric Therapeutics (OPT) | Office of the Commissioner (OC) | US FDA

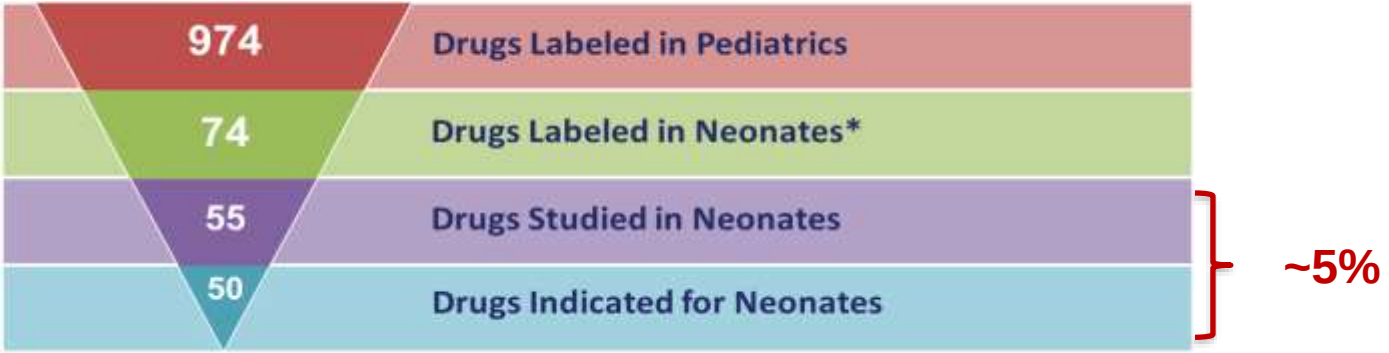
Overview: Clinical Pharmacology Considerations for Neonatal Studies – February 15, 2023

Overview

- Background and scope of the guidance
- Definitions of neonatal subpopulations
- Special considerations for conducting clinical studies in neonates
- Ethical considerations

Neonatal Studies are Needed

- Majority of drugs used in neonates is "off label"[1]



- Scientific (& legislative) mandate to address gaps
  - Marketed products approved for other populations
  - New products for treatment of neonatal conditions

[1]*Laughon et. Al., JAMA Pediatr 2014*

Neonatal Studies are Challenging

- Rapid development of organs and tissues
- Ontogeny of enzymes, receptors, transporters, neurotransmitters
- Complex transitional physiology
- Comorbidities

The Scope of the Guidance

This guidance addresses:

- Clinical studies to support neonatal drug development (i.e., INDs, NDAs, BLAs)
- Effectiveness, safety, dose-finding studies that include assessment of clinical pharmacology information (e.g., PK, PD)

This guidance does not address:

- Timing to initiate neonatal studies relative to the overall clinical development program for a drug/biologic

Definitions

- The *neonatal period*[1] is defined as:
  - the day of birth plus 27 days (for the term and post-term newborn)
  - the day of birth through the expected date of delivery plus 27 days (for the preterm newborn)
- Post-menstrual age (PMA) dates a gestation from the first day of the mother's known or reported last menstrual period
- Gestational age (GA) = PMA at birth
- Postnatal age (PNA) = chronological age after birth
- Neonatal age group includes individuals up to 44 weeks PMA

[1] *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population (April 2018)*

Subgroup Classifications

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
- 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

Subgroup Classifications

Based on weight at birth:

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

Other Classifications

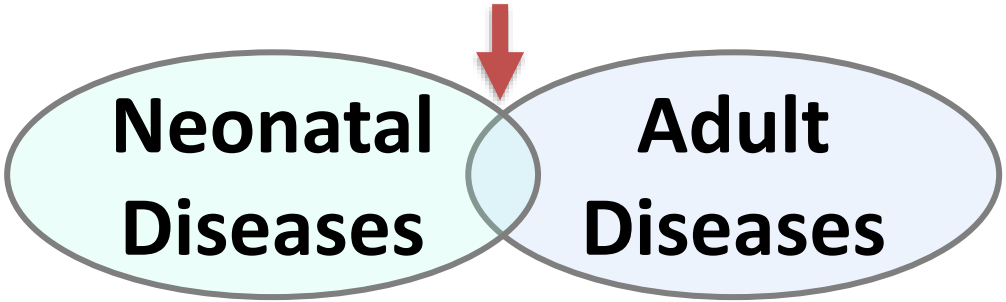
- Intrauterine growth restriction (IUGR): Fetal weight (by ultrasound) < 10^{th} %ile
- Small for gestational age (SGA) neonates: Birth weight < 10^{th} %ile
- Large for gestational age (LGA) neonates: Birth weight > 90^{th} %ile

Importance of Classifications

- Use for stratification to address heterogeneity
- Characteristics are not interchangeable
  - GA/PMA reflects developmental maturity
  - PNA reflects transitional physiology which changes rapidly after birth
  - BW impacts allometric scaling
  - Growth disturbances (e.g., SGA or LGA) impact developmental physiology & pharmacology

Establishing Substantial Evidence of Effectiveness

- Adequate and well-controlled studies
- Pediatric extrapolation[1]



[1]*ICH Harmonised Guideline on Pediatric Extrapolation E11a, Draft guidance April 2022*

Establishing an Adequate Safety Database

- Experience in other populations
- Seriousness of adverse reactions
- Rarity of condition
- Unique vulnerabilities of the neonate

Study Design Considerations

- Clinical variability in the study population
- Limitations of neonatal blood sampling
- Multi-stakeholder input (clinicians, nurses, parents, patients) to inform study design and feasibility
- Safety data should be collected with consideration of neonatal-specific AE definitions/classifications[1]

[1]*Salaets et. al., Arch Dis Child 2019*

Ethical Considerations

- 21 CFR part 50, subpart D - *Additional Safeguards for Children in Clinical Investigations*
- Neonatal expertise represented on IRB/DSMB

Refer to *Ethical Considerations for Clinical Investigations of Medical Products Involving Children - Guidance for Industry, Sponsors, and IRBs* (draft guidance, September 2022)

Challenge Question #1

Which of the following statements is NOT true?

A. Term and post-term neonates are born at or greater than 37 weeks gestation

B. Extremely low birth weight neonates (ELBW) describes infants weighing <1000 g at birth

C. Gestational age, postmenstrual age and postnatal age may be used interchangeably, and studies should adjust for just one of these factors

D. Adequate and well-controlled studies in a neonatal population may not always be required to establish substantial evidence of safety and effectiveness of a drug for regulatory approval

Summary

- The majority of drugs used in neonates have not been adequately assessed in the neonatal population
- Drug development in neonates faces unique challenges due to rapid developmental changes and vulnerabilities characteristic of the neonatal period
- Neonatal clinical pharmacology studies should be designed considering information known from other populations, clinical variability of the neonatal subpopulation(s), and ethical safeguards

Clinical Pharmacology of Neonates and Considerations for Study Design

Elimika Pfuma Fletcher
Policy Lead and Senior Clinical Pharmacologist
Office of Clinical Pharmacology (OCP) | Office of Translational Sciences (OTS) | CDER | US FDA

Overview: Clinical Pharmacology Considerations for Neonatal Studies - February 15, 2022

Outline

- General clinical pharmacology considerations
- PK, PD and other assessments
- Study design considerations
- Modeling Informed Drug Development (MIDD)

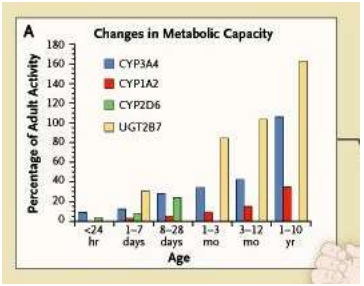
Clinical Pharmacology Considerations

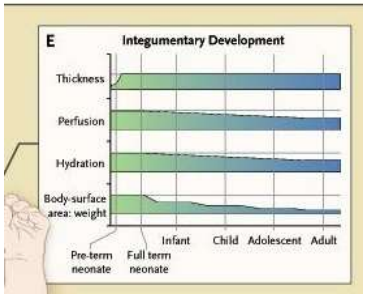
- Limited PK, PD, disease information in neonates
- Differences in PK and potentially in PD and safety compared to adults and older children
- Variability in PK across the neonatal period
- Limited blood volume for sampling
- Specific considerations related to drug administration and formulations

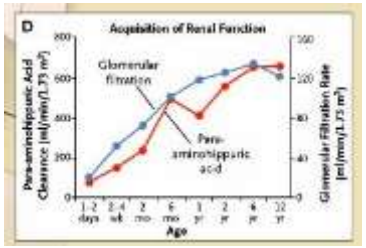
PK Characterization

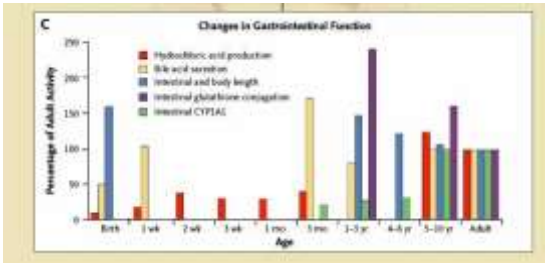
Evaluate PK in a wide spectrum of PMA/PNA

- Variability across neonates - body size, maturation, illnesses, concomitant medications
- Absorption - ontogeny (GI, skin) and other (administration methods, enteral feeding)
- Distribution - body composition, protein and tissue binding
- Metabolism
- Excretion - GFR, transporter ontogeny





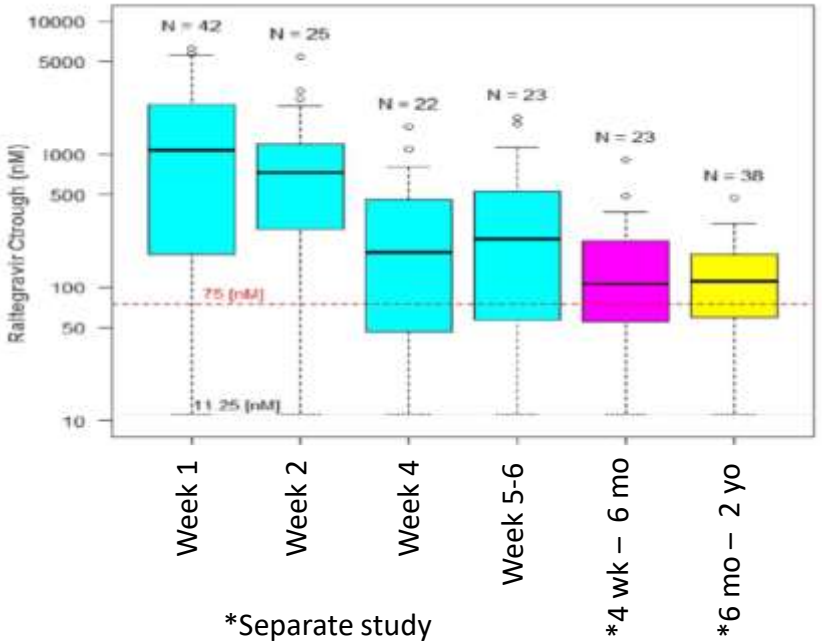




Kearns et al. 2003

Example 1: Raltegravir

- UGT1A1 substrate - rapid increase in UGT1A1 activity and drug clearance after birth
- Neonatal Study: 1.5 mg/kg QD (**week 1**), 3 mg/kg BID (**weeks 2 to 4**) and 6 mg/kg BID (**weeks 5 and 6**)
- Exposures were deemed comparable to those observed in adults and older pediatrics



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Pharmacodynamics (PD)

- Analyze PD in addition to PK, whenever possible
- PD can be effect on biomarker or clinical endpoint
- Ontogeny in target tissues may alter the PK/PD relationship
- Early discussion with FDA in considering relevant PD/biomarker for a study

Pharmacogenomics

- Genetic differences can affect PK, PD, safety or efficacy
- The relationship between genomic profiles and developmentally regulated gene expression has not been extensively studied in the neonatal population
- Evaluate pharmacogenomics within a study when known PGx effects for the drug

PMID: 20223877 and 35795337

Immunogenicity

- Immunogenicity for some products can impact PK, PD, safety or efficacy
- Immune response differs in neonates compared to older pediatrics and adults
- For relevant products (e.g., therapeutic proteins), assess immunogenicity in the study with neonates

https://doi.org/10.1016/j.immuni.2017.03.009

Outline

- General clinical pharmacology considerations
- PK, PD and other assessments
- **Study design considerations**
  - Dose selection
  - Formulation
  - Sample size
  - PK sampling and bioanalysis
- Modeling Informed Drug Development (MIDD)

Dose Selection

- Use all available data to inform starting dose in neonates - MIDD
- Rapid growth and maturity could mean dose adjustments within a short period of time – Consider ontogeny, PMA and PNA
- Consider titration of dose, adaptive trial design, TDM within a study
- Different dosing regimens can be studied
- If FIH study is in neonates, early discussion with FDA is needed to determine approach for dose selection

Dose Selection

- Consider PMA and PNA
- Can differ by drug

Table 3: Dosage in Neonates (less than or equal to 28 days of postnatal age) for Bacterial Meningitis and Septicemia

Gestational age (weeks)	Postnatal age (days)	Dosage
less than or equal to 34	less than or equal to 7	100 mg/kg/day in equally divided doses every 12 hours
less than or equal to 34	greater than or equal to 8 and less than 28	150 mg/kg/day in equally divided doses every 12 hours
greater than 34	less than or equal to 28	150 mg/kg/day in equally divided doses every 8 hours

Pediatric Age group	Initial Dose	Maximum Dose	Duration of infusion
Birth to 2 years of age (including preterm and term neonates)	0.5 to 1 g/kg/day Increase the dose by 0.5 to 1 g/kg/day	3 g/kg/day	20 to 24 hours for preterm and term neonates 12 to 24 hours for patients 1 month to 2 years

*PMA = GA at birth

Table 3: Dosing Regimens for Pediatric Patients with PMA less than or equal to 32 weeks, or greater than 32 weeks to less than or equal to 40 weeks

PMA (weeks)	Dose (mg/kg)	Dosing Interval (hours)
Less than or equal to 32	5	8
Greater than or equal to 32 weeks to less than or equal to 40	7	8

1. Ampicillin: Docket FDA-2015-N-2342
2. Lipid emulsion: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/207648s005lbl.pdf
3. Clindamycin: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208083s006s007s008lbl.pdf

Formulation

- Age-appropriate formulation is needed
- For safety, consider excipients and volume
  - volume should consider parenteral nutrition and SOC drugs
- Study should capture information related to potential interactions with tubing or co-administered fluids/nutrition
- Consider potential differences in absorption for non-IV administration

Sample Size

- Sample size should consider variability and precision needed for the relevant PK or PD endpoints
- Consider having adequate numbers across the subpopulations (PMA/PNA)
- Clinical trial simulations combining data from various sources can inform sample size

Blood Samples

- Limit to the least possible blood sample volume required
- Account for blood drawn for routine clinical assessment + what is needed for the study (several published guidelines on limits)
- Potentially time with clinical blood draws (opportunities for use of scavenged samples - with careful planning and adequate storage conditions)
- Careful consideration when illness impacts Hgb (can set minimum levels for blood draw)
- Sparse sampling is a practical approach to limit amount of blood drawn

Justification is needed for sampling schedule and number of samples

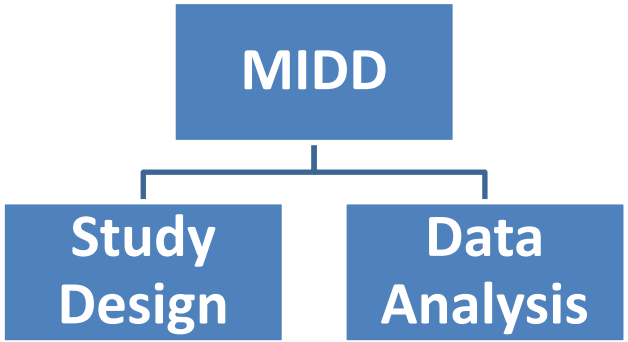
PK Sampling and Analysis

- Consider PK sampling at a separate site than the administration site
- Use a validated bioanalytical method - accurate, precise, sensitive, specific, and reproducible
- Use of alternative sampling (microsampling) or alternative matrices (e.g. urine) should account for any bias in concentrations. Should be
  - discussed with the agency
  - supported from a bioanalytical perspective

Outline

- General clinical pharmacology considerations
- PK, PD and other assessments
- Study design considerations
- **Modeling Informed Drug Development (MIDD)**

Model Informed Drug Development (MIDD)



- Use all available information
- Data: MOA, PK, ontogeny
- Sources of data: animal models, in vitro and in vivo studies (literature and sponsor conducted)
- Approaches include Pop PK, PK/PD, PBPK

Example 2: Maraviroc

Previous Information	Submission	MIDD

• PK, PD, safety and efficacy data
  ○ in adults
  ○ ≥ 2 years old
• Studies included patients on interacting CYP3A inhibitors
• Labeled with weight-tiered dosing in peds > 10 kg
	• Open label PK and safety study in birth to 6 weeks of age
	• No CYP3A inhibitor use in trial
		• Supported dose by weight tiers in > 2 kg
		• Interpolation of dosing 6 weeks – 2 years of age
		• Deemed insufficient to support dosing in <10 kg with CYP3A inhibitors

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Summary

- Adequate clinical pharmacology characterization in neonates is key for optimal dose selection
- Neonates are a diverse population and careful consideration is needed for study planning
- MIDD approaches can inform dose selection and study design

CE Question

MIDD approaches can be used to support drug development in neonates by informing

a) dose selection

b) study design

c) instructions of use

d) all of the above

Resources

- General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products Guidance for Industry | FDA
- General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products | FDA
- Ethical Considerations for Clinical Investigations of Medical Products Involving Children | FDA
- E11A Pediatric Extrapolation | FDA
- Medical products for newborns | FDA
- Congressional Act that addresses neonates as part of Title V of the Food and Drug Administration Safety and Innovation Act (FDASIA)
- Safety, dosing, and pharmaceutical quality for studies that evaluate medicinal products (including biological products) in neonates | Pediatric Research (nature.com)
- Drug Labeling and Exposure in Neonates | Critical Care Medicine | JAMA Pediatrics | JAMA Network
- Development of a neonatal adverse event severity scale through a Delphi consensus approach | Archives of Disease in Childhood (bmj.com)
- http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/09/WC500255440.pdf (EMA draft concept paper)
- EMA Guideline on the Investigation of Medicinal Products in the Term and Preterm Neonate

Closing Thought

- Neonates need therapies that are safe and effective for conditions relevant to them.
- Careful planning and innovative approaches that consider the variability and vulnerability in the population are needed to achieve this.

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Questions?