Formulation Development for Neonate Patients –Rising to the Challenge

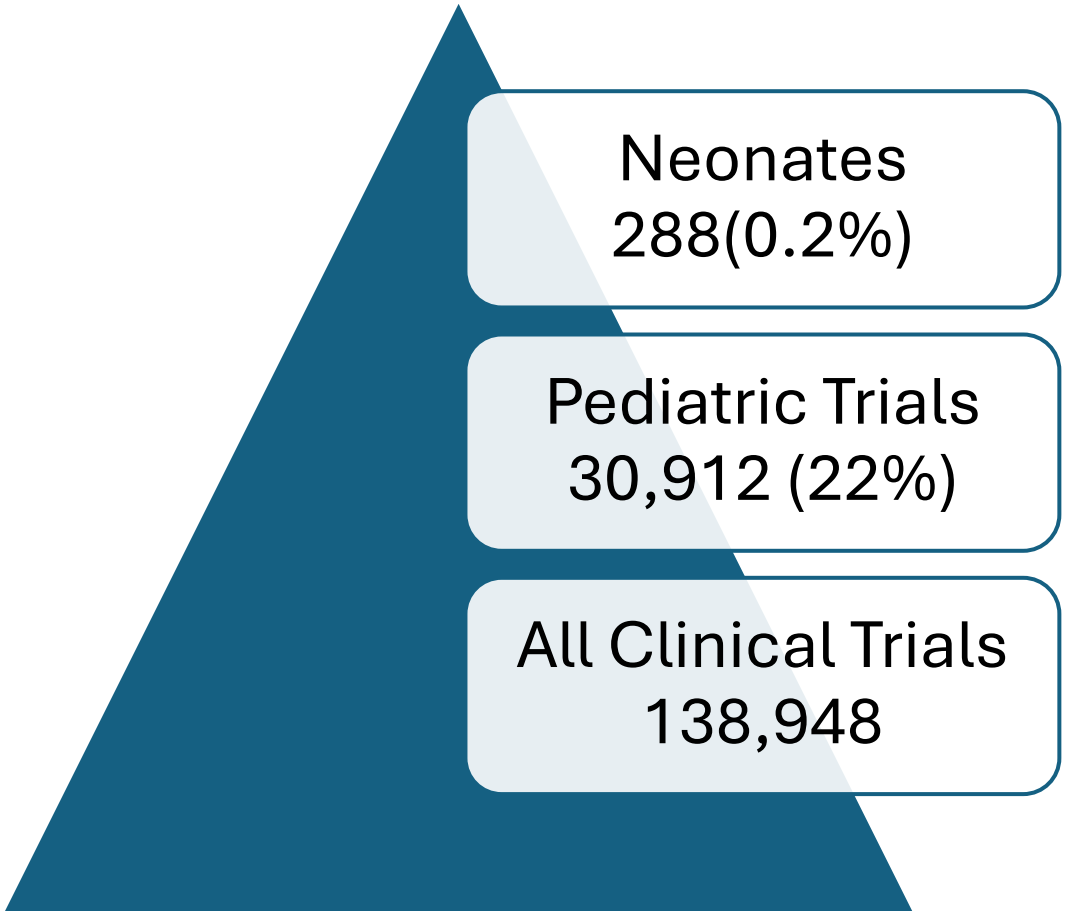
Karen C Thompson

Merck & Co., Inc., Rahway, NJ, USA

- “Newborns were one of the last therapeutic orphans to be adopted”
- Stiers and Ward, JAMA Pediatric **168,** 106-108 (2014)

Incidence of Clinical Studies with Neonates

Pansieri et al. Arch. Dis. Child. Fetal Neonatal Ed. **99**, F438 (2014).



The Neonatal Patient

- Neonatal period:
  - Period from birth up to and including 27 days in term neonates, or from birth up to a post-menstrual age of 40 weeks and 27 days in preterm neonates. Weight range 0.5 to 5 kg

Post Term Neonate	Term Neonate	Preterm Neonate	Very Preterm Neonate	Extremely Preterm Neonate
➢ 42 weeks GA	37-42 weeks GA	<37 weeks GA (=/<36 weeks and 6 days gestation	28-32 weeks GA	<28 weeks GA

GA Gestational age is the measure of how far along a pregnancy is, counted in weeks and days from the first day of the last menstrual period

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

Subgroup Classifications

Based on weight at birth

Preterm Neonates	Extremely low birthweight neonates	Very low birth weight neonates	Low birth weight neonates
<600 g	<1000 g	<1500 g	<2500 g

Neonate weight ranges 500 g-5000 g

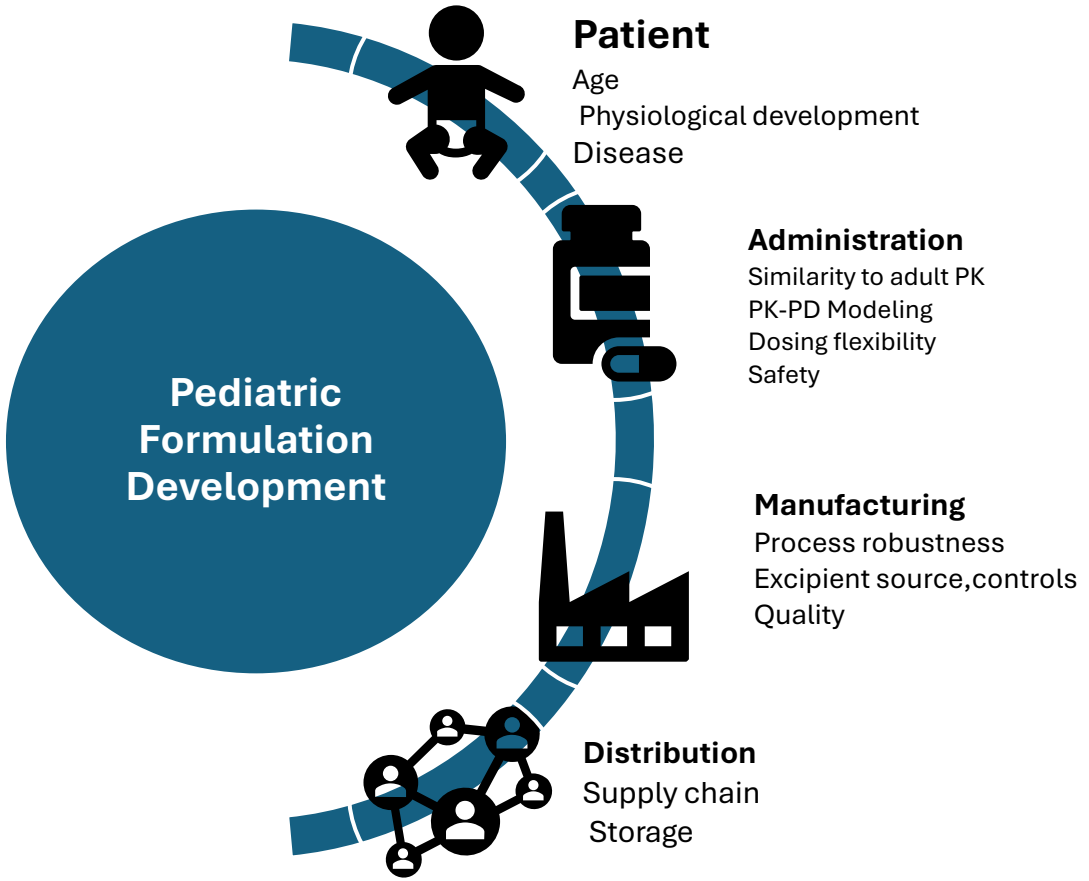
Ref **Dionna Green, MD, FCP**
Overview: Clinical Pharmacology Considerations for Neonatal Studies – February 15, 2023

Importance of Classification

- Stratification to address population heterogeneity
- Characteristics are not interchangeable
- GA/PMA reflects developmental maturity
- Post birth age reflects transitional physiology which changes rapidly after birth
- Body weight impacts allometric scaling
- Growth disturbances impact developmental physiology and pharmacology

Ref Dionna Green, MD, FCP
Overview: Clinical Pharmacology Considerations for Neonatal Studies – February 15, 2023

Multiple Inputs Driving Pediatric Formulation Development.



Neonate Physiology and impact on formulation development

- Elimination
- Gastric function and motility
- Intestinal permeability
- Drug distribution
- Drug metabolism

Design of the Raltegravir Formulation

- No preservatives
- Taste masked Ethylcellulose/Hypromellose coating
- Banana flavor
- Powder for suspension
- Combination product with instruction of use, mixing cup, dosing syringes
  - Supported with HF studies
- Flexibility to dilute to provide adequate volumes for administration to the neonate population (adjustment in reconstitution needed to address reduced doses for neonates)

Development with consideration of Pediatric Patients

- Pregnant women living with HIV have increased risk for delivering a low birth weight (LBW) neonate (birth weight less than 2500 g)
  - Overall frequency worldwide 14.6%
    - Lancet Glob Health 2019, 7(7), e849-860.
  - Rates of LBW neonates for mothers living with HIV as high as 41% in South Africa and 34% in India.
    - BMC Pregnancy Childbirth 2015, 15:246.
    - South African Journal of Infectious Diseases 2018, 33(2), 42-45.

Further study Raltegravir in Low Birth Weight/premature Neonates

- The raltegravir Postnatal raltegravir clearance was slower in preterm neonates than full term neonates
- Primarily metabolized by uridine diphosphate glucuronosyltranferase 1A1 (UGT1A1)
  - Low activity at birth increasing 100 fold during the first 14 weeks of life
  - Avoiding excessive raltegravir plasma concentrations is important because it can compete with unconjugated bilirubin for binding to albumin.

  - Ref Diana Clarke et al, J. Acquir Immune Defic Syndr.2020 Dec 15, 85(5) 626-634

Raltegravir Pediatric Dosing

- The pediatric dosing for raltegravir is based on the patient's weight and age. Here are the general guidelines for pediatric dosing:

- **Neonates (birth to 1 week of age)**: 1.5 mg/kg/dose.
- **Neonates (1 to 4 weeks of age)**: 3 mg/kg/dose.

- **Pediatric patients (4 weeks of age and older)**: 6 mg/kg/dose twice a day.
  - **10 kg to less than 14 kg**: 75 mg twice daily.
  - **14 kg to less than 20 kg**: 100 mg twice daily.
  - **20 kg to less than 25 kg**: 150 mg twice daily.
  - **25 kg or more and unable to swallow a tablet**: 400 mg twice daily.
  - **25 kg or more and able to swallow a tablet**: 400 mg twice daily.

- Appendix A: Pediatric Antiretroviral Drug Information - Raltegravir | NIH

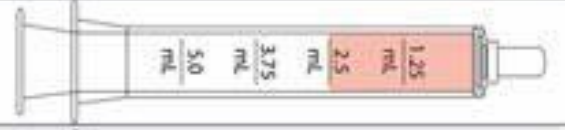
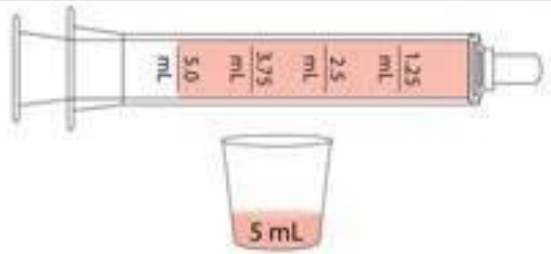
Raltegravir Powder for Suspension

ISENTRESS®
raltegravir

Combination product development the development of a booklet for instructions for use, color coded syringes to add in product constitution and administration. Instructions to aid in accurate syringe dosing.

Dosing Flexibility for Pediatric Patients

Liquid dosing– Flexibility with an oral syringe

WEIGHT (Pounds)	AGE (Estimated)	DOSE Liquid for Children	
6-11 lbs	0-3 months	1.25 mL (1/4 tsp)	
12-17 lbs	4-11 months	2.5 mL (1/2 tsp)	
18-23 lbs	12-23 months	3.75 mL (3/4 tsp)	
24-35 lbs	2-3 years	5 mL (1 tsp)	

The Work Continues

Neonates present a challenge for formulators and clinicians due to population heterogeneity.

As we develop treatments for this population and shared knowledge on developmental physiology impacting drug metabolism and elimination we provide critical knowledge for PK modeling to better serve this population.