Improving Health Outcomes for High Risk Neonates via Safer Therapeutic Intervention

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On behalf of the DART Technical Committee
The Problem

• 90% NICU drugs are used off-label
• Often treated with multiple medicines at the same time
• Adverse drug effects (ADEs) 3x more likely
• NICU patients have the highest medical errors and ADE rates (sparse data on correct use of medicines)
• Very few therapies are being developed for neonates
• Prematurity rates:
  • EU: 5-10%
  • USA: 12% (worst of any developed country; 131st in the world)
Therapeutic Orphans: The Drug Development Disconnect

- Neonatal studies are regarded as not needed
- Disease does not occur in newborns (but does in 1 yr olds)
- Are neonatal studies too difficult?
  - Ethical, emotional concerns
  - Knowledge gaps in nonclinical models of neonatal diseases
  - Endpoints do not apply or cannot be measured in newborns
  - PK difficult to measure in newborns, need new formulations
  - Study designs for pediatrics do not fit newborns e.g., smaller # patient population
- Should limit studies in newborns based on AE in adults, assuming they occur in neonates (e.g., QTc?)
Addressing the Disconnect: Ongoing Efforts

Provides direction on the nonclinical safety studies important to support a pediatric development program. It will recommend standards for the conditions under which nonclinical juvenile animal testing is considered informative and necessary to support pediatric clinical trials and provide guidance on the design of the studies. (Draft Guideline developed Sept 2018.)

PRECLINICAL

DART Technical Committee
- Emerging Issues proposal submitted in 2014
  - Nonclinical Efficacy and Safety Studies to Support Neonatal Therapeutics
- Adopted by DART Committee in 2015
  - Extensive nonclinical expertise within the committee
  - Leveraged connections to bring in external expertise

CLINICAL

Regulatory requirement for a Pediatric Study Plan (FDA) and Pediatric Investigational Plan (EMA) needed before submission of New Drug Application or Marketing Authorization Application.
- Food and Drug Administration Safety and Innovation Act (FDASIA) 2012
- European Commission Pediatric Regulation No 1901/2006
✓ Identify relevant animal models for developmental stage or disease condition of preemie/neonate
  • What models are available?
  • What aspect of the condition do they model effectively?
  • What is the limitation of the model?

✓ Provide knowledge of the pharmaco-dynamics during development

✓ Assess long term effects of acute & chronic treatment on development & outcome
- Frame the basic principles for evaluating new animal models to address key therapeutic questions in neonates

- Increase understanding of comparative physiology development between neonates and nonclinical animal species

- Identify relevant models of neonatal disease and explore therapeutic options and strategies

- Demonstrate where nonclinical models can inform dose selection in neonates through case studies

- Survey of existing models

- Neonate physiology

- Starting dose

- Research framework

- Key therapeutic areas:
  - Neonatal brain injury
  - Neonatal lung injury
  - Neonatal abstinence syndrome
  - Retinopathy of Prematurity
  - Neonatal sepsis

- Health and Environmental Sciences Institute
  Science for a Healthier World

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Neonatal Drugs: A Snapshot of the Regulatory Landscape

- 28 drugs studied in neonates (US)

- 1 in 4 PIPS specifically mention neonatal development (Europe)

- Inclusion of neonates increased from PIPs:
  - 15% - 25% in 2008
  - 24% - 32% in 2011


*There are 24 neonatal labeling changes involving 23 drugs. Linezolid has 2 labeling changes.*
Neonate Physiology

*Increasing the understanding of comparative physiological development between neonates and nonclinical animal species*

- ADME of oral/systemic medicines
- Age of patient or animal
- Selection of animal model
- Drug efficacy and toxicity
  - Species
  - Maturational age changes (physiology)
  - Ontogeny profiles of enzyme, transporters, nuclear receptors
Neonate Physiology:
Increasing the understanding of comparative physiological development between neonates and nonclinical animal species

Overview
De Schapedrijver et al. 2019. Drug Metab Dispos.
Completed

Brain
Will be integrated to second phase (case studies)

Cardiovascular
Hausner et al. 2019. Drug Metab Dispos.
Completed

Liver
In progress
Anticipated completion in Summer 2019

Kidney
In internal & HESI reviews

Gastrointestinal
Completed;
Kluever et al. 2019. Drug Metab Dispos.
Research Framework:
Framing the basic principles for evaluating existing and developing new models to address key therapeutic questions in neonates

What are the basic principles for the construction of an animal model to study questions in neonates?

How can we help guide researchers to work with existing nonclinical models or establish new models to further research these diseases and support clinical development and success of future therapies?
1. Performed literature searches to identify available nonclinical models for 6 diseases affecting neonates:

- Neonatal brain injury
- Neonatal abstinence syndrome
- Neonatal lung injury
- Retinopathy of Prematurity
- Neonatal sepsis
- Neonatal GI injury

2. Completed summaries of available nonclinical models for each disease:

- How well does the model capture the key clinical hallmarks of each disease?
- What is the species and model relevance to humans?
- What is the model application: mechanism, efficacy, and/or safety?

3. Make integrated assessment:
   - Are there common elements among the neonatal disease models or specific elements for each disease state?
   - Summarize the gaps in information that animal models cannot address
   - Provide recommendations for researchers working in these areas

4. Inform and promote future research!

   - INC clinicians identified the most common NICU conditions (premature birth not within current scope of work)
   - Research into nonclinical models to complement INC work on clinical aspects
Many of the evaluated models are geared towards investigating mechanisms and/or efficacy.

- Much less focus on safety

Various species used with clear preference for rodents.

- Sheep, pig and primates appear to be useful for some of the neonatal diseases but not widely used

In many cases it seems that treatments that are effective in animal models do not translate to efficacy in the clinic.

- Reflection of inherent species and developmental differences
- Lack of standardized protocols (methodological concerns)
- Lack of understanding of mechanisms underlying the disease

No single animal model completely covers the complexity of the human condition.

- May need a combination of models to cover all aspects of a particular disease

Points to consider when developing a new disease model:

- Physiological similarities/differences between species
- Understanding strengths and limitations
- Model must effectively capture the precipitating human event / early aspects of the disease
- Consider the goal of the research
- Need to pick an age when the target organ in the animal model is at the same developmental stage as in the neonate
Starting Dose:

Demonstrate where nonclinical models can inform dose selection in neonates through case studies

• White paper, building on recent INC clinical pharmacology paper, to address leveraging all sources of info to optimize dose selection for neonates, taking into account prenatal and postnatal physiology
  • Adult studies
  • Pediatric studies
  • Non-clinical and juvenile studies
  • *In vitro* studies
  • *In silico* models
## Overview of Case Studies

### Key Components

<table>
<thead>
<tr>
<th>Disease status</th>
<th>Clinical ADME characteristics</th>
<th>Target dose animal model information needed</th>
<th>in vitro model info needed</th>
<th>Clinical data information available</th>
<th>Known trial design considerations</th>
<th>Final Case Studies:</th>
</tr>
</thead>
</table>
| • Is it related to children or adults? | • Disease mechanism  
• Significant ADME considerations?  
• Additional safety info needed? | • Adult animal model?  
• Juvenile animal model?  
• Maturational toxicity known? | • Reflective of neonatal ADME  
• Reflective of neonatal state? | • Adult data available?  
• Pediatric data available?  
• Safety and PK/PD info in neonates available? | • Is the info in labels? | • Meropenum  
• Clopidogrel  
• Caffeine  
• Synthroid  
• Surfactant |
Drug Disease Similar in Neonates and Adults

May Be Able to Extrapolate Some Efficacy Data From Adult

Examine Drug ADME to Support Dose in Neonates

Match PK/PD and Obtain Safety Data

Drug Approved in Adults

Drug with Potential Use in Neonates

Drug Disease Related but not Similar in Neonates and Adults

May Need Additional Animal Models of Disease to Support Dosing and Efficacy (Usually Juvenile)

Examine Drug ADME to Support Dose in Neonates

Match PK/PD and Obtain Clinical Efficacy and Safety Data

Off-Label Use Based on Empirical Estimation of Dose

May Have PK information but no Associated PD or Clinical Efficacy

Need to encourage these studies!!
**Clinical Development Plan**

- **Phase 1 Trials** in Healthy Volunteers are not ethical in Pediatric Patients and May Not be Possible in Adults Depending on the Route of Administration and Potential Toxicity.

- **Phase 2 Trials** for Proof of Concept and Safety May Need to be Done in Neonates with the Disease or Condition.

- **Drug Not Approved in Adults**
  - Animal Models of Disease to Support Dosing and Efficacy (Usually Juvenile)
    - Need to Link Mechanism of Action of the Drug to Underlying Pathophysiology of Human Disease
    - Need to Develop Animal Models Specific for Neonatal Diseases

- **Animal Model Mechanism of Action of Drug**
  - Need to Use an Animal Model Where the Drug ADME is Similar to Human

- **Examine Drug ADME and Potentially Use Modeling to Support Dose in Neonates**
  - Match Animal PK/PD and Obtain Clinical Efficacy and Safety Data

- **Synthroid**
  - Phase 1 Trials in Healthy Volunteers Not Ethical in Pediatric Patients and May Not be Possible in Adults Depending on the Route of Administration and Potential Toxicity

- **Surfactant**
  - Phase 2 Trials for Proof of Concept and Safety May Need to be Done in Neonates with the Disease or Condition
Key Takeaways

• Dosing strategies are difficult for neonates

• Juvenile animal models can be used to:
  • Understand mechanism of action of the drug and ontogeny of organ systems to predict on/off-target effects
    • Role of metabolizing enzyme systems
  • Models of clinical disease
    • Dose ranging studies
    • Proof of concept studies
    • Safety studies
  • PBPK modeling

• Need to develop more *in vitro*, *in vivo*, and *in silico* models to help optimize dosing strategies for first in human trials in neonates
Next Steps

- Large compendium of information published and in-press:
  - Symposia
  - CE or other educational courses

- Primary audiences
  - Preclinical
  - Clinical
    - Int’l Neonatal Consortia
    - American Academy of Pediatrics

- Other next steps will also be informed by ICH S11 conversations
SURVEY OF EXISTING MODELS
NEONATE PHYSIOLOGY
STARTING DOSE
RESEARCH FRAMEWORK

Right Drug
Right Population
Right Dose
Right Trial Design
Right Endpoints

http://www.cfda.gov/activities/programs/clinical_trials/clinicalTrials Consort returns:
http://www.upmc.edu/ctp/pharmacokinetics.cfm
http://www.wfshbp.org/activities/featurestory/current-issue/archive-single/should-we-accept-enrichment-designs-in-psychiatry-ac3a3b97ef270e4b82eda25c825e9b.html
http://www.acse1.org/pharmacometrics/theory.html
Thanks to ...

<table>
<thead>
<tr>
<th>Overall Project Leads:</th>
<th>Survey</th>
<th>Physiology</th>
<th>Research Framework</th>
<th>Dose</th>
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</thead>
<tbody>
<tr>
<td>Karen Davis-Bruno (US FDA)</td>
<td>Vijay Umaliya (Janssen)</td>
<td>Luc de Schaepdrijver (Janssen)</td>
<td>Sarah Campion (Pfizer)</td>
<td>Suzie McCune (US FDA)</td>
</tr>
<tr>
<td>Luc de Schaepdrijver (Janssen)</td>
<td>Susan Laffan (GSK)</td>
<td>Pieter Annaert (U Leuven)</td>
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**INDUSTRY**
- AbbVie, Inc.
- AstraZeneca AB
- Biogen Inc.
- Boehringer-Ingelheim GmbH
- Celgene Corporation
- Charles River Laboratories
- Chiesi Pharmaceuticals*
- Covance, Inc.
- Eli Lilly and Company
- Genentech
- GlaxoSmithKline
- Hoffmann-La Roche
- Janssen Pharmaceuticals
- Merck & Co. Inc.
- Pfizer, Inc.
- Sanofi
- Takeda Pharmaceutical Company Limited

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- Health Canada
- Karolinska Institute*
- Medicines and Healthcare Products Regulatory Agency (UK)
- Medicines Evaluation Board (The Netherlands)
- National Agency of Medicine and Health Products Safety (ANSM, France)*
- National Institute for Public Health and the Environment (RIVM, The Netherlands)
- National Institute of Environmental Health Sciences
- National Toxicology Program
- US Food and Drug Administration

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- Ghent University*
- McMaster University
- Radboud University, Nijmegen Medical Centre*
- University of Leuven*

**CONSULTING/RESEARCH**
- Aclario Pharmaceutical Developmental Group, Inc.
- Critical Path Institute
- Exponent, Inc.

*new organizations to HESI DART