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Proposal title:

Nonclinical efficacy and safety studies in support of neonatal pediatric therapeutics use and development

Key words: (*minimum of two*)

Neonates, efficacy, safety, therapeutics, drug, nonclinical models; pediatrics; drug development

Describe the problem to be addressed. Why is the issue important? To whom is this issue important?

Children represent a unique and dynamic patient population for administration of therapeutics. Pediatrics are not simply small adults when considering drug therapy. Neonates and premature infants are a special population within the pediatric population. During the neonatal period there are specific physiological differences between neonates and their more mature pediatric counterparts. Significant differences in glucose and thermoregulation, neurologic, cardiopulmonary and immunologic development and responses have been documented across species. While drug therapy in neonates is infrequent, when it is needed it must be administered with consideration of the special circumstances these patients present. Neonates, particular premature neonates present with unique disease conditions that cannot be extrapolated from adult disease. The reality is that for the majority of drugs available, therapeutic dosing is an estimated guess and safety information is based on clinical anecdotes. Up to 90% of the drugs used in the neonatal intensive care unit (ICU) are used off-label¹. As a result, pediatrics are three times more likely to be associated with an adverse drug event (ADE)². Neonatal ICU patients have the highest medication errors and potential ADE rates.

Drug development typically utilizes nonclinical *in-vitro/in-vivo* models to support efficacy and safety. This is particularly important in support of neonatal safety where significant data gaps exist in our understanding. Identification and/or development of new nonclinical models representative of this rapidly evolving patient population are warranted. Neonatal nonclinical models and/or disease models may be useful in establishing safety/efficacy for a particular therapeutic and appropriately designed nonclinical animal model studies may be designed to address the long-term safety of necessary therapeutics. Clinical trials in neonates are typically short-term and are not designed to identify long-term developmental outcomes.

The focus of this proposal is to explore and identify neonatal animal models which would provide needed information on proof of concept (efficacy) and safety of neonatal drug therapy for their unique disease

¹ Emmerich J, Dumarcet N, Lorence A. (2012) N Engl J Med 367:1279-81

² Fortescue E et al. Pediatrics (2003) 111(4):722-9

Kaushal R et al. JAMA (2001) 285:2114-20



issues. This project would potentially benefit public health; provide needed information to fill in some data gaps for the neonatal pediatricians who treat this public health sector as well as regulated industry and global regulatory agencies.

Describe the basic project steps or stages to the best of your ability, including an expected timeline, milestones, and deliverables for the first two years.

Year 1:

1. Develop an expert group to identify the major gaps in neonatal (pre-term and term neonates) drug development.
2. Identify an expert group to convene to address how to best leverage neonatal nonclinical models to support safety and proof of concept for neonatal drug therapy. Identify any effort ongoing in the field. Get their contribution.
3. Explore relevant neonatal nonclinical models for human neonatal disease
4. Identify/develop relevant study designs and data that can be obtained from such studies
5. Explore how the data obtained from relevant neonatal animal models can be extrapolated to human neonates and identify any relevant examples

Year 2:

6. Explore the relevance and any modifications of these identified neonatal nonclinical models of human neonatal disease to premature infants and their therapeutic needs
7. Extrapolate lessons learned from the steps above to first in pediatric or pediatric only drug development
8. Publish a review of the expert working group's findings and analysis

What is the potential or anticipated impact of successfully achieving the milestones described above? (Describe scientific, regulatory, policy, public health, and/or other impacts.)

Since up to 90% of the drugs used in the neonatal ICU are used off-label more information is needed to appropriately treat this special pediatric population safely. Nonclinical models have been used to address issues that cannot be addressed ethically or technically in clinical trials. This proposal will provide necessary background information to address some of these data gaps in treating the neonatal human health need. Specifically this project will identify relevant neonatal nonclinical models and appropriate study designs that will provide initial proof of concept for pediatric only therapeutics as well as identify long-term developmental safety hazards. Neonatal clinical studies are typically 18-24 months duration. While this is longer than most pediatric clinical studies, it is not long enough to assess any potential adverse effect on maturity. This information is not readily or ethically obtained from clinical experience in neonates and is necessary to ensure safe and efficacious therapy for a pediatric population with special needs. A relevant animal model which matures at a more rapid rate than human neonates (condensed development) may serve to assess human risk in this regard. Such animal models have been used successfully in the past in development of neonatal only products e.g. lung surfactants.



Describe the interdisciplinary, collaborative nature of the proposed project, and identify potential partners: *(identify institutions, organizations, companies, and or consortia)*

Pharmaceutic and biopharmaceutical industry
Academic and industry experts in teratology and developmental toxicology
Clinical neonatologists, pediatricians
FDA/CDER including Div. Pediatric & Maternal Health, Rare Diseases, Inborn Error, pediatricians & toxicology specialists
EPA
EMA