Drug-Induced Cardiac Abnormalities in Premature Infants and Neonates

Luana Pesco Koplowitz, MD, PhD
DUCK FLATS Pharma, LLC
Elbridge, NY

Barry Mangum, PharmD, FCP
Duke University Medical Center
Durham, NC

White Paper Proposal Background

- Originally presented at the December 2013 annual meeting.
- Formal Project Submission to the CSRC occurred in 1st Q 2014
- Committee formed and initially convened late 2nd Q 2014
- White paper focus and major headings are established
- Presently, an extensive literature search and summation has reached late stages and initial writing is set to begin
- 1st Draft is expected by 3rd Q 2015

Committee Member Composition

Thirteen Members from Canada and the United States

- Canada
  - Health Canada - 1

- United States
  - FDA - 4
  - Academia - 2
  - Industry - 6

Areas of Expertise include:

Nonclinical, clinical pharmacology, clinical pediatric medicine, cardiology and neonatology

White Paper Overview

As initially proposed:

- Assessment of medications that can cause cardiac abnormalities
- Identification of physiological differences found in premature infants and neonates that cause greater susceptibility to drug-induced cardiac events
- Pharmacological mechanisms of action of common cardiac toxicities

White Paper Overview

(continued)

- Pharmacological animal models of cardiovascular drug effects in premature infants and neonates
- Common congenital conditions which can exacerbate drug-induced cardiac adverse events
- Assessments of alternate treatments which can minimize cardiac adverse events

Document Format and Focus

- Format adheres to the *American Heart Journal* guidelines
- Content has been driven by literature search results
  - To date, over 175 literature references have been identified
  - References are summarized for committee review and for potential inclusion

Document Format and Focus

(continued)

Content Outline

- ABSTRACT
- INTRODUCTION
- OVERVIEW OF HUMAN DEVELOPMENTAL CARDIAC, ANATOMY, AND PHYSIOLOGY
- NON-CLINICAL (IN VIVO, IN VITRO) MODELS IN JUVENILE ANIMALS
  - CARDIOVASCULAR
  - CENTRAL NERVOUS SYSTEM
  - IMMUNOLOGY/ONCOLOGY
  - ANTI-MICROBIALS
  - PULMONARY

Document Format and Focus

(continued)

- RETINOID
- GLANDULAR
- RETINOPATHY

- DRUG-INDUCED CARDIAC TOXICITY PREMATURE INFANTS AND NEONATES BY (DRUG) THERAPEUTIC AREA
  - Cardiovascular
  - Central Nervous System (CNS)
    - Anticonvulsants
    - Analgesics/Anesthetics
    - Anti-Depressant/Anti-Anxiety/Sedatives
    - Stimulants

Document Format and Focus

(continued)

- Immunology/Oncology
  - Anti-Retrovirals
  - Chemotherapeutic agents
- Steroid and nonsteroidal anti-inflammatory drugs (NSAIDs)
- Anti-Microbials
- Pulmonary
- Formulation Excipients
  - Polysorbate 80
  - Benzyl Alcohol
  - Polypropylene Glycol

Document Format and Focus

(continued)

- CISAPRIDE
- (Dr. Mangum to write)
- WHAT WE DON'T KNOW
- List areas that need to be studied
  - Bioanalytical Assay
    - Therapeutic range for drugs
    - Other topics need further discussion