Drug-Induced Cardiac Abnormalities in Premature Infants and Neonates

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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
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
• 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
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
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
• 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