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
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
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