Special Considerations and Utility of Modeling and Simulation for Pediatric Medical Countermeasures:

Introduction

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Background

- ***Threat**:* chemical, biological, radiological, and nuclear (CBRN) agents and emerging infectious diseases (EID)
- ***Medical countermeasures (MCMs):*** pharmaceutical (e.g., vaccines, drugs, antibodies) and non-pharmaceutical (e.g., masks, ventilators) products intended to diagnosis, prevent, treat, and/or mitigate the health effects of threat agents
- ***FDA's role:*** protect the U.S. from CBRN and EID threats by ensuring that MCMs to counter them are safe, effective, and secure; facilitate MCM development and availability

Background

- ***MCM Initiative (MCMi):*** FDA initiative to respond to a call from the President and the Secretary of Health and Human Services; launched 2010
  - Pillar 1: Enhance the MCM review process -- Promote development and availability of MCMs by establishing clear regulatory pathways
  - Pillar 2: Advance regulatory science -- Maintain a robust MCM regulatory science program to create the data necessary to support regulatory decision-making
  - Pillar 3: Optimize and modernize the legal, regulatory, and policy framework to establish effective policies and mechanisms to facilitate timely access to available MCMs
- ***Includes emphasis on addressing at-risk populations (e.g., children)***

Source: U.S. Food and Drug Administration
Medical Countermeasures Initiative Strategic Plan 2012-2016

Children represent an *at-risk* population in the event of a CBRN or EID incident

- Specific physiologic and developmental characteristics place children at risk of greater exposure and harm:
- ***Airborne toxins:*** increased minute ventilation; lower to the ground
- ***Transdermal toxins:*** less keratinized, more permeable skin; relatively larger body surface area
- ***Infectious agents:*** immature immune system
- ***Food/water contaminants:*** higher dose of toxicant per pound of body weight

Challenge: 40% of the CBRN MCMs in the SNS have not been approved for any pediatric use

- ~60% of MCMs in the Strategic National Stockpile (SNS) have been approved for use in children
  - ~38% have been approved for children of all ages (e.g., ciprofloxacin, atropine, raxibacumab)
  - ~22% have been approved for some, but not all, pediatric age groups (e.g., Prussian blue)

- ***Existing gaps:*** age or size-adjusted dosing regimens and age-appropriate formulations

****Note: FDA can authorize the use of MCMs by populations or for indications that are unapproved under an EUA or IND protocol**

Source: U.S. Government Accountability Office Report
National Preparedness: Efforts to Address the Medical Needs of Children
In a Chemical, Biological, Radiological, or Nuclear Incident, April 2013

Challenge: there are ethical obstacles to safely evaluating MCMs in children

- ***Additional Safeguards for Children in Clinical Investigations (21 CFR 50 Subpart D):***
  - Restricts research in children to involve either "minimal" or a "minor increase over minimal" risk absent a potential for direct benefit to the child, or must present risks that are justified by anticipated direct benefits to the child; the balance of which is at least as favorable as any available alternatives
- ***The Presidential Commission for the Study of Bioethical Issues concluded:***
  - Pre-event pediatric MCM research – which offers no prospect of direct benefit since participants are not affected by the condition being studied – generally cannot proceed unless it is minimal risk
  - Prior to conducting “minimal risk” studies in children, the risk must be identified and characterized through prior testing such as modeling, testing in animals, and studies in adults

Source Presidential Commission for the Study of Bioethical Issues, Safeguarding Children: Pediatric Medical Countermeasure Research, March 2013

MCM Product Availability or Approval

- ***Emergency Use Authorization (EUA), IND, fast track, priority review, accelerated approval***
- ***The Animal Rule***: provides a regulatory mechanism to approve products when human challenge studies are not ethical or feasible
  - FDA may grant marketing approval based on adequate and well-controlled animal studies when the results of those studies establish that the drug or biological product is reasonably likely to produce clinical benefit in humans
  - Demonstration of product safety in humans is still necessary
- The Animal Rule applies equally to pediatrics and adult populations

****Note: 5 products have been approved under the animal rule (pyridostigmine bromide--2003, cyanokit--2006, levofloxacin--2012, raxibacumab--2012, botulism antitoxin heptavalent 2013)**

Source: Guidance for Industry: Animal Models – Essential Elements to Address Efficacy Under the Animal Rule, Draft Guidance, January 2009

The Animal Rule – Requirements

1) Pathophysiology of the disease and product's mechanism of action are reasonably well understood;

2) The product efficacy is demonstrated in more than one animal model, unless animal model is sufficiently well characterized for predicting the response in humans;

3) The animal study endpoint is clearly related to the desired benefit in humans (e.g., survival, prevention of major morbidity); and

4) The data or information on product pharmacokinetics and pharmacodynamics in animals and humans allow selection of an effective human dose

Source: Guidance for Industry: Animal Models – Essential Elements to Address Efficacy Under the Animal Rule, Draft Guidance, January 2009

Scenarios for Determining An Effective Human Dose

- ***Repurposed products:***
  - Prior PK and safety data for another use in adults and/or pediatrics
- ***New molecular entities (NMEs):***
  - PK and safety in healthy adults; likely no clinical data in pediatrics

Utility of Modeling and Simulation for Pediatric MCMs

- Has the potential to leverage all prior information through data integration using PK, PK-PD or PBPK-PD models
- Applicability in reducing residual uncertainty at each step?
  - Inter-species extrapolation; adult to pediatric extrapolation
    - Assumption = similar exposure, similar effectiveness
  - Human dose selection
  - Ontogeny and maturation
  - Predictions of benefit-risk
  - Formulation performance

Recent MCM Approvals in Children: Supported by Modeling & Simulation

- ***Levofloxacin*** – 2008; 2012
  - Treatment of inhalational anthrax
  - Treatment of plague
- ***Raxibacumab*** – 2013
  - Treatment of inhalation anthrax in combination with appropriate antibacterial agents
  - Prevention of inhalational anthrax when alternative therapies are not available or not appropriate

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