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**
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)**
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

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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