Leveraging Novel Technologies to Develop Pediatric Medical Countermeasures

Thomas Colatsky
Division of Drug Safety Research
Center for Drug Evaluation and Research

Workshop on Pediatric Development of Medical Countermeasures: Ethical and Regulatory Considerations
February 15-16, 2012
Special Challenges: Pediatric MCMs

- Incomplete data sets
- Knowledge gaps
- Need to predict
  - Natural history and mechanisms of biothreat-induced diseases not fully characterized in pediatric subjects
  - Most non-clinical studies with bioterrorism agents are conducted in adult animals
  - Few (if any) pediatric safety or efficacy biomarkers currently available to monitor the field use of medical countermeasures
  - Available data are dispersed in public, regulatory, other sources → need to integrate knowledge, map interactions, and predict outcomes
From Scaling to Prediction

Non-Clinical Data

PATIENT

PBPK models
PK/PD models

EFFICACY?
DOSE?

TREATMENT

BIOMARKERS?

PATHOGEN

Targets / Pathways ?

DISEASE

Mechanisms / Pathways ?

MECHANISTIC MODELS

Response
Modeling Biological Systems

What it can do:

- Conceptualize the system
- Codify current facts
- Test competing hypotheses
- Identify controlling factors
- Estimate inaccessible system variables
- Predict system response under new conditions

Mechanistic Modeling

- Assumes that biology is hierarchical, and that different biological states reflect interactions of multiple interconnected processes
  - *Sum is greater than the individual parts*
  - *Concept of “emergent properties”*
- Integrates basic knowledge about chemical and biological processes underlying system response
- Contains generalizable information against which study data sets can be tested
- May be built “top down” or “bottom up”
Top-down vs. Bottom-Up Models

Integrated system response

Top-down

Patient response
Clinical trials

Disease processes
Therapeutic effects
Adverse events

Toxicity pathways
Efficacy pathways

Bottom-up

“Parts list”: genes, molecules

Approaches?

- **Knowledge building**
  - New experimental disease and treatment data
  - Text mining / natural language processing
  - Linked cheminformatics and bioinformatics
    - Structure-based searching of biological data
  - Interaction mapping

- **Model Building**
  - (Q)SAR models
  - Extended PBPK and PK/PD models
  - Mechanistic models
  - Scaling and scenario testing
Goals/Outcomes

- Searchable knowledge base of biological threat agent mechanisms, disease processes and treatment structures/pharmacology
- Predictive (Q)SAR and disease models
  - Augmented PBPK and PK/PD models
- Treatments and treatment combinations with enhanced safety/efficacy
  - Pathway analysis → treatment synergies
- Disease progression and/or remission biomarkers for the pediatric population
  - Experimental + informatics approaches
  - Use to estimate/scale doses and monitor efficacy