University of California
San Francisco
UCSF
School of Pharmacy

FDA Workshop

Pediatric Trial Design and Modeling:

Moving into the next decade

PM Session: Model Informed Pediatric Drug Development and Simulation

September 8, 2017, Washington DC,

Modeling and Clinical Trial Simulation in Drug Development

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UCSF, NDA Partners

A Little History of M&S in Academia, Drug Development & Regulation

- **'30'- 60's**: PK, PBPK theory
- **'70's – 80's**
  - Yaffe, Levy, Jusko PK in pediatric studies
  - Sheiner, Beal et al @ PK forecasting; pop PK, PK Screen, PKPD, software (Nonlin, NONMEM etc)
- **'90's**:
  - 1st Clin Trial Simulations (Hale @ Mycophenylate + RCCT)
  - Software – SimCyp, R
  - FDAMA: Peds, Single trial approval, '98 Evidence of Effectiveness guidance
  - FDA guidances
    - Pop PK, E-R, ICH E-4
- **'00-present**:
  - Industry, FDA/EMA uptake of M&S Clin Trials - ICH E-11, 11(R1)
  - Extrapolations
  - Adaptive trials, MCP-Mod
  - M&S–based labeling support

Regulatory M&S Guidance (Pediatric M&S)

- **ICH Guidelines**
  - E-11 (2000)
    - N_{min} & sampling times @ Pop PK, sparse sampling @ optimal sampling theory
- **E-11 (R1) (2016)**
  - Use of Existing Knowledge (**no mention of Bayesian inference**)
  - Extrapolation
  - Clinical trial simulation
    - **No mention of PBPK or Bayesian methods**
- **EMA Guidelines**
  - Clinical trials in small populations PK/PD modeling**, Bayesian methods**
  - Ethical considerations for clinical trials with the pediatric population
    - **Adaptive design**

Considerations for Going Forward

- **Incorporation of prior knowledge**
  - Bayesian adaptive trial designs
  - Bayesian networks
  - Bayesian inference for regulatory review & approval of safety and effectiveness
    - Phase out frequentist null hypothesis testing
- **Employment of estimands in effectiveness trials**
- **New Guidances**
  - That Teach (e.g. CDRH Bayesian Methods)
    - PBPK methods
    - Bayesian methods for drugs & biologics
- **Education**
  - PBPK, Bayesian inference, Evidence Assessment, Decision Analysis
- **Labeling**
  - Articulate probability of effectiveness

END