Modeling and Clinical Trial Simulation in Drug Development

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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

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Regulatory M&S Guidance (Pediatric M&S)

• **ICH Guidelines**
    • $N_{\text{min}}$ & 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**

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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