Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches
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Nonregulatory Perspective:

Challenges and Opportunities to Enhance Model Sharing upon Regulatory Use

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Disclaimer

- I am a consultant for NDA Partners, a ProPharma company.
- I champion modeling and simulation to medical product developers and regulatory scientists
- I am a member of a research team that is exploring alternative statistical models for evaluation of bioequivalence and comparative bioavailability data

What kind of models are we talking about ?

- PK Models
  - Compartmental
  - PBPK
- PD Models
- Exposure-Response Models
- Disease Models
- Statistical Models

Nonregulatory Perspective
Why use a model ?

- *Potential* benefits:
  - Shorter development time
  - More efficient development efforts
  - Lower cost of development
  - Facilitation of communications with the Agency
  - Increased potential for approval
- *Potential* barriers:
  - Lack of understanding of modeling and its value
  - Lack of expertise for implementation
  - Longer development time
  - Greater resource requirements and cost
  - Uncertainty of success potential

Precedents
Shared Disease Models

- Two 1-sided t-test (TOST) for bioequivalence approval
- CDER Division of Pharmacometrics Disease Model Program
  - 16 vetted disease models
    - Utilities include dosage optimization, trial design, extrapolations across populations, etc
  - 14 related publications
- Example Applications:
  - Disease models for schizophrenia, bipolar I disorder, and partial onset seizure can be used to support efficacy findings in adults which can be directly extrapolated into pediatric patients – without undertaking a clinical efficacy trial in children.
    - Guidance: Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 2 Years of Age and Older Guidance for Industry, https://www.fda.gov/media/130449/download

No	Disease Model	Usage
1	Non-small cell lung cancer model [1]	Late phase clinical trial design
2	Parkinson's disease model [2]	Endpoint selection and clinical trial design
3	Alzheimer's disease model [3]	Endpoint selection and clinical trial design
4	Diabetes disease model [4]	Clinical trial design
5	Huntington's disease model [5]	Patient enrichment and clinical trial design
6	Duchenne muscular dystrophy disease model [6]	Patient enrichment and clinical trial design
7	Human immunodeficiency virus model [4]	Clinical trial design
8	Schizophrenia model [7]	Pediatric extrapolation
9	Bipolar I disorder model [8]	Pediatric extrapolation
10	Weight loss model [9]	Clinical trial design
11	Bone density model [10]	Clinical trial design
12	Idiopathic pulmonary fibrosis model [11]	Patient enrichment and clinical trial design
13	Rheumatoid arthritis model [12]	Endpoint selection and clinical trial design
14	Pulmonary arterial hypertension model [13]	Endpoint selection and clinical trial design
15	Breast cancer model	Clinical trial design
16	Seizure model [14]	Pediatric extrapolation

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What are challenges in sharing and using models ?

- Modeling expertise and understanding of the value of models of sponsor and FDA staff
  - A work in progress
- Willingness of sponsors
  - Perceived Risks – failure, competition
  - Cost in time and $$
- Championship and receptivity of FDA staff

What are opportunities to enhance model sharing ?

- Recruitment of knowledgeable sponsor and FDA staffs
- Education of sponsor and FDA decision-makers
- Promotion, encouragement and championship
- Published examples of successful shared models
- Procedures and initiatives
  - EOP2a meetings
  - MIDD, CID pilot programs