Model-Informed Drug Development: Past, Present, Future

Issam Zineh, PharmD, MPH
Office of Clinical Pharmacology
Office of Translational Sciences | CDER | US FDA
Huntington’s Disease Regulatory Science Consortium (HD-RSC)
Silver Spring, MD, November 6, 2017
Acknowledgments

Office of Clinical Pharmacology
- Atul Bhattaram (Pharmacometrics)
- Elizabeth Ford (Regulatory Affairs)
- Kevin Krudys (Pharmacometrics)
- Rajnikanth Madabushi (Guidance and Policy)
- Kimberly Maxfield (Executive Program and Project Management)
- Jose Ruiz Vicente (Applied Regulatory Science)
- Yaning Wang (Pharmacometrics)
- David Strauss (Applied Regulatory Science)

Center for Devices and Radiological Health
- Tina Morrison (ASME V&V40 Subcommittee)

NB: My views will be CDER-centric.
Model-Informed Drug Development

• “Development and application of pharmaco-statistical models of drug efficacy and safety from preclinical and clinical data to improve drug development knowledge management and decision-making” (Lalonde)

<table>
<thead>
<tr>
<th>Indication</th>
<th>MBDD approach adopted</th>
<th>Efficiencies gained over historical designs and analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolism*</td>
<td>Omit phase IIa, model-based dose–response relationship, adaptive phase IIb design</td>
<td>2,750 Fewer patients, 1 year shorter study duration</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Model-based dose–response relationship</td>
<td>1,000 Fewer patients</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Prior data supplementation, model-based dose–response relationship, sequential design</td>
<td>760 Fewer patients, 1 year shorter study duration</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Prior data supplementation, model-based dose–response relationship</td>
<td>120 Fewer patients, 1 year shorter study duration</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>Model-based dose–response relationship</td>
<td>1,025 Fewer patients</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Model-based dose–response relationship</td>
<td>437 Fewer patients, increased probability of success</td>
</tr>
<tr>
<td>Global anxiety disorder</td>
<td>Omit phase IIb</td>
<td>260 Fewer patients, 1 year shorter study duration</td>
</tr>
<tr>
<td>Lower urinary tract symptoms</td>
<td>Meta-analysis</td>
<td>Increased probability of success</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Meta-analysis</td>
<td>Increased probability of success</td>
</tr>
</tbody>
</table>

MBDD, model-based drug development.

• Pathway for lowering drug attrition and dealing with regulatory uncertainty

Critical Path Opportunities List

TOpic 1: Better Evaluation Tools
TOpic 2: Streamlining Clinical Trials
TOpic 3: Harnessing Bioinformatics
TOpic 4: Moving Manufacturing into the 21st Century
TOpic 5: Developing Products to Address Urgent Public Health Needs
TOpic 6: Specific at-Risk Populations — Pediatrics

Experimental Models • Statistical Models • Empirical Models • Mechanistic Models • Simulations

N=76 Opportunities
N=17 Model-related
Regulatory Science
Science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products

Vision
FDA will advance regulatory science to speed innovation, improve regulatory decision-making, and get products to people in need. 21st Century regulatory science will be a driving force as FDA works with diverse partners to protect and promote the health of our nation and the global community.
1. **Modernize toxicology to enhance product safety**
   1. Develop better models of human adverse response
   2. Identify and evaluate biomarkers & endpoints that can be used in non-clinical + clinical evaluations
   3. Use and develop computational methods and in silico modeling

2. **Stimulate innovation in clinical evaluations and personalized medicine to improve product development and patient outcomes**
   1. Develop and refine clinical trial designs, endpoints, and analysis methods
   2. Leverage existing and future clinical trial data (including for disease progression modeling)
   3. Identify and qualify biomarkers and study endpoints
   4. Develop a virtual physiologic patient

3. **Harness diverse data through information sciences to improve health outcomes**
   1. Develop and apply simulation models for product lifecycles, risk assessment, & other reg sci uses
   2. Analyze large scale clinical and preclinical datasets
   3. Incorporate knowledge from FDA regulatory files into a database integrating a broad array of data types to facilitate development of predictive toxicology models and model validation
   4. Develop new data sources and innovative analytical methods and approaches

4. **Facilitate development of MCM to protect against threats to health**
   1. Develop, characterize, and qualify animal models for MCM development
   2. Modernize tools to evaluate MCM product safety, efficacy, and quality
   3. Develop and qualify biomarkers of diseases or conditions
# MIDD: Sampling from Neuroscience

<table>
<thead>
<tr>
<th>Disease</th>
<th>Objective</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson's Disease</td>
<td>Develop disease progression and drop out models</td>
<td>Inform trial design; novel endpoints</td>
</tr>
<tr>
<td>Alzheimer's Disease</td>
<td>Develop disease progression and drop out models</td>
<td>Inform CAMD DDT</td>
</tr>
<tr>
<td>Huntington’s Disease</td>
<td>Develop disease progression model</td>
<td>Inform trial design (enrichment)</td>
</tr>
<tr>
<td>Partial Onset Seizures</td>
<td>Compare E/R between adult and pediatric patients</td>
<td>Waive pediatric efficacy studies (&gt;4 yo) for adult-approved products</td>
</tr>
<tr>
<td>Duchenne Muscular Dystrophy</td>
<td>Develop disease progression model</td>
<td>Inform trial design (inclusion criteria)</td>
</tr>
</tbody>
</table>
Evolution of MIDD in OCP

1990 – 2000
Early Days
IVIVC, PK-PD
POPPK
Pharmacometrics Group

2000 – 2010
Rapid Growth
POPPK, D/R, E/R
Guidance
CTS and disease models
Early days of PBPK research and application
Division of Pharmacometrics (DPM)

2010 – Now
Approaching Mainstream
Routine application of pharmacometrics, PBPK for DDIs
Early applications of semi-mechanistic and mechanistic modeling in review and research
Opportunistic standardization
Regulatory acceptance of DDTs
Organizational growth, assimilation and prioritization

2017 – Beyond?

Adapted from R. Madabushi, OCP
Integrated View of Modeling in Drug Review

**Chemistry models**
- SAR safety alerts
- ADME prediction

**Exposure models**
- Dosing
- TK/evaluation
- PBPK
- Human PK/PD Prediction

**Mechanistic Models**
- Targets / pathways
- Toxicity mechanisms
- Disease mechanisms
- System response
  - (cell, organ, patient)

**Preclinical**

**IND**

**Clinical**
- DDI
- PK/PD
- Dose escalation
- Dose ranging

**NDA**
- Signal confirmation
  - (6 mo. safety review)

**Post-Approval**
- PK/PD Bridging
  - Pediatrics
  - Elderly
  - Dosage forms

**Knowledge integration**
- Toxicity prediction
- Risk evaluation
- Risk translation
- Drug-disease interactions
- Drug-patient interactions

**Statistical analysis**

**Graphical representation**

**Biomarkers**
- Study endpoints
- Disease progression

**Clinical trial data**
- Efficacy/Safety

**Signal confirmation**
- Patient response
- Risk:benefit assessment

Courtesy T. Colatsky
MIDD: From Concept to Application

PBPK

Application of Physiologically Based Pharmacokinetic (PBPK) Modeling to Support Dose Selection: Report of an FDA Public Workshop on PBPK

C. Wagner, P. Zhao, Y. Pan, Y. Hsu, J. Gordo, S.M. Huang, and Y. Sinta

A New Perspective in the Field of Cardiac Safety Testing through the Comprehensive In Vitro Proarrhythmia Assay Paradigm


PBPK model components

Drug-dependent component

Drug-drug interactions

Receptor binding

Protein binding

Drug transport

Active transport

Passive diffusion

ADME, PK, PD, and MOA

Drug metabolism

Sodium

Calcium

Potassium

Integrate ion channel effects

Predict clinical risk of arrhythmias

Check for unanticipated effects

Integrating ion channel effects

1. In vitro Assessment of Drug Effects in Multiple Ionic Currents

2. In silico Computer Modeling to Predict Risk

3. In vitro effects on Human Stem Cell Derived Ventricular Cardiomyocytes

4. In vivo ECG Biomarker in Phase 1 Clinical Trials

EKG

Baseline

Drug

PMIDs: 21191381, 26225246, 24747236, 26170255, 24336137, 28986934
MIDD Enablers and Disablers: Two Sides of the Same Coin

- Environment
- Acceptance of MIDD approaches
- Resources /Budget
- Structure/focus/awareness
- Evolution of regulatory processes
- Process and guidance
- Technical advancement

- Acceptance of MIDD approaches
- Environment
- Resources /Budget
- Structure/focus/awareness
- Evolution of regulatory processes
- Process and guidance
- Technical advancement
Evolution of MIDD at OCP

1990 – 2000
Early Days
IVIVC, PK-PD, POPPK Pharmacometrics Group

2000 – 2010
Rapid Growth
POPPK, D/R, E/R, Guidance CTS and disease modeling, Early days of PBPK research and application Division of Pharmacometrics (DPM)

2010 – Now
Approaching Mainstream
Routine application of Pharmacometrics, PBPK for DDIs Early applications of semi-mechanistic and mechanistic modeling in review and research Opportunistic standardization Regulatory acceptance of DDT Organizational growth, assimilation and prioritization

2017 – Beyond Accepted Standard
Development of standards for data, analyses, and processes Pathways for dedicated regulatory engagement Integration of various M&S activities throughout the drug development and organization Management of information and knowledge – disease modeling, PBPK 2.0 Incorporation of newer approaches and technologies – QSP, Bayesian, etc. Leveraging RWD

Adapted from R. Madabushi, OCP
Commissioner’s Blog on *In Silico* Tools

- **Innovation Initiative**
- Use of in silico tools in clinical trials for improving drug development and making regulation more efficient
- M&S to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse event mechanisms
- Creation of natural history databases to support model-based drug development

Increased Focus on Advancing Regulatory Science

1993-1997: PDUFA I
Review backlog

1998-2002: PDUFA II
Review times and procedures

2003-2007: PDUFA III
Increased interaction; support for post-market safety

2008-2012: PDUFA IV
Enhance pre-market review; modernize post-market safety system

2013-2017: PDUFA V
Review+ comms enhancement; strengthen regulatory science & post-market safety; electronic data standards

2018-2021: PDUFA VI
Program/process enhancement; HR; IT; enhance regulatory science & promote innovative tools

Modified from J. Barton, OSP/CDER/FDA
PDUFA 6: Regulatory Decision Tools

- Complex Innovative Trial Designs
- Model-informed Drug Development
- Biomarker Qualification
- Real World Evidence
- Benefit/Risk Assessment
- Patient Voice
Opportunities for MIDD
PDUFA VI – Enhancing Regulatory Decision Tools To Support Drug Development and Review

• Advancing Model-Informed Drug Development
  – FDA will develop its regulatory science and review expertise and capacity in MIDD approaches
  – FDA will convene a series of workshops to identify best practices for MIDD. Topics include PBPK, design analysis and inferences from dose-exposure-response, disease progression model development, immunogenicity
  – FDA will conduct a pilot program for MIDD approaches. For sponsors participating in the pilot program, FDA will grant a pair of meetings specifically designed for this pilot program
  – FDA will publish draft guidance, or revise relevant existing guidance, on model-informed drug development
  – FDA will develop or revise, as appropriate, relevant MAPPs or SOPPs, and/or review templates and training, to incorporate guidelines for the evaluation of MIDD approaches.

Problem Identification and Resolution

Problem Identification

Use within review process

Recommend scientific solutions

Develop public standards

Recommend scientific solutions

Use within review process

Develop public standards

Use within review process

Develop public standards

Adapted from Critical Path Report 2004
Impact of Collaboration

MAPP 4100.2
CDER Staff Participation in Public Private Partnerships (PPP) and Consortia

<table>
<thead>
<tr>
<th>Impact</th>
<th>PPP Impact Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updates on Pediatric Medication Safety</td>
<td>2</td>
</tr>
<tr>
<td>Support of Regulatory Actions (Approvals, Recalls)</td>
<td>2</td>
</tr>
<tr>
<td>New Clinical Trial Designs</td>
<td>3</td>
</tr>
<tr>
<td>Drug Development Tool Qualification</td>
<td>7</td>
</tr>
<tr>
<td>Drug Development Tool Letter of Support</td>
<td>10</td>
</tr>
<tr>
<td>Support of Industry Guidances</td>
<td>12</td>
</tr>
<tr>
<td>White Paper PubMed Citations</td>
<td>≥1000</td>
</tr>
</tbody>
</table>

Adapted from K. Maxfield, OCP | Maxfield 2017 [PMID 28776943]
Risk-Informed Credibility Framework

In order to more fully leverage computational modeling and simulations for medical products and clinical care, we need a methodology to ensure appropriate credibility.

**Credibility**: the trust, through the collection of evidence, in the predictive capability of a computational model for a context of use.

---

**Model risk** is the possibility that the computational model leads to an incorrect decision that results in patient harm and/or other undesirable impacts.

- **Model influence** is the contribution of the computational model relative to other available evidence in making a decision.

- **Decision consequence** is the significance of an adverse outcome resulting from an incorrect decision.

---

Courtesy T. Morrison, CDRH | ASME V&V40 Subcommittee
Conclusion

• MIDD has exhibited impressive growth over the past several decades with notable expansion over the last 5-10 years

• Growing appreciation for the theoretical and actual benefits of MIDD has created an important moment to advance MIDD

• Recent legislation and maturing of MIDD-related programs can set the direction re: MIDD for the foreseeable future

• Enablers and disablers exist and must be appreciated in strategic planning for MIDD

• Evidentiary considerations and stakeholder expectations must be addressed, and can be through multi-disciplinary collaboration