Role of Disease Models in New Drug Development and Approval

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Best Practices for Development and Application of Disease Progression Models
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Outline

• Introduction (MIDD and Disease-Drug-Trial Model)
• Disease Models at FDA and Case Examples
  – Disease Models at FDA
    (DPM Strategic Goals and Examples of Disease Models)
  – Case Examples
    • Pediatric Extrapolation: Schizophrenia Disease-Drug-Trial Model
    • Patient Selection: DMD Disease Model
    • Biomarker Change with Disease: Osteoporosis Disease-Drug Model
• Interaction with FDA on Disease Modeling
  – FPP Program
  – MIDD Paired Meeting Pilot Program
  – CID Program
• Opportunities for Collaboration
• Take Home Message
Quantitative Disease-Drug-Trial Models

Natural Progression Biomarker vs. Outcome

Exposure-Response for Efficacy & Safety

Drop Out

Model-Informed Drug Development

Development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources to address drug development or regulatory issues*

QSAR: Quantitative structure–activity relationship
QSPR: Quantitative structure–property relationship

* From PDUFA 6; Excludes statistical designs involving complex adaptations, Bayesian methods, or other features requiring computer simulations to determine the operating characteristics of a confirmatory clinical trial.
Pharmacometrics 2020 Strategic Goals

- Implement 15 Standard Templates
- Develop 5 Disease Models
- Train 20 Pharmacometricians
- Design By Simulation
- Integrated Quantitative Clinical Pharmacology Summary
- International Harmonization
# Disease Model Examples from FDA

<table>
<thead>
<tr>
<th>No</th>
<th>Disease Model</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NSCLC Model [^1]</td>
<td>Late Phase Trial Design.</td>
</tr>
<tr>
<td>2</td>
<td>Parkinson's Disease Model [^2]</td>
<td>Endpoint Selection and Clinical Trial Design</td>
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<tr>
<td>3</td>
<td>Alzheimer's Disease Model [^3]</td>
<td>Endpoint Selection and Clinical Trial Design</td>
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<td>4</td>
<td>Diabetes Disease Model [^4]</td>
<td>Clinical Trial Design</td>
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<td>5</td>
<td>Huntington's Disease Model [^5]</td>
<td>Patient Enrichment, Clinical Trial Design</td>
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<td>6</td>
<td>DMD Disease Model [^6]</td>
<td>Patient Enrichment, Clinical Trial Design</td>
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<td>HIV Model [^4]</td>
<td>Clinical Trial Design</td>
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<td>8</td>
<td>Schizophrenia Model [^7]</td>
<td>Pediatrics Extrapolation</td>
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<td>Bipolar I disorder Model [^8]</td>
<td>Pediatrics Extrapolation</td>
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<td>Weight Loss Model [^9]</td>
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<td>Bone Density Model [^10]</td>
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<td>12</td>
<td>Idiopathic Pulmonary Fibrosis Model [^11]</td>
<td>Patient Enrichment, Clinical Trial Design</td>
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<td>13</td>
<td>Rheumatoid Arthritis Model [^12]</td>
<td>Patient Enrichment, Clinical Trial Design</td>
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<tr>
<td>14</td>
<td>Pulmonary Arterial Hypertension Model [^13]</td>
<td>Endpoint Selection and Clinical Trial Design</td>
</tr>
</tbody>
</table>

Case 1: Disease Model for Schizophrenia
Characterize the Profile of the Disease Progression and ER
Qualitative Evidence to Demonstrate Disease Similarity

Disease Model

Disease Progression over a Typical 6-Week Trial is Similar Between Adults and Adolescents Completers (Observed)

\[ PANSS(t) = \text{Baseline PANSS} \times \left[ 1 - P_{\text{max}} \times \left( 1 - \exp\left(-\frac{t}{\text{PD}}\right)^{\text{P}0\text{\_D}} \right) \right] \]
## Justification for Exposure Response Similarity

### Drug Model

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age (yrs)</th>
<th>Dose in Adolescents (mg/day)</th>
<th>Dose in Adults (mg/day)</th>
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<tbody>
<tr>
<td>Paliperidone ER</td>
<td>12-17</td>
<td>Weight &lt;51 kg: 3-6 Weight &gt;51 kg: 3-12</td>
<td>3-12</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>13-17</td>
<td>400-800</td>
<td>400-800</td>
</tr>
<tr>
<td>Risperidone</td>
<td>13-17</td>
<td>1-6</td>
<td>4-16</td>
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<tr>
<td>Aripiprazole</td>
<td>13-17</td>
<td>10-30</td>
<td>10-30</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>13-17</td>
<td>40-80</td>
<td>40-160</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>13-17</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

### Graph

**Drug A**

- **Predicted (Adults)**
- **Observed (Pediatrics)**

**Axes:**
- **X-axis:** AUC at Steady State (mg x hr/L)
- **Y-axis:** Double Delta in Total PANSS at Week 6

**Note:**
- The graph illustrates the comparison between predicted and observed values for Drug A across different AUC levels.

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**References:**
Extrapolation of Efficacy from Adults to Pediatrics

Schizophrenia Program

Drugs with Similar MoA
Extrapolation of Efficacy

Drugs with New MoA
Inclusion of Pediatrics in Adult Registration Trials

*Juvenile animal studies needed for bipolar I indications less than 12 years of age

**Open label safety studies could concurrently enroll patients with bipolar I and schizophrenia adult and pediatric patients

Pharmacokinetic Study

Placebo-Control, Parallel Fixed Dose Design

Open Label Safety Study

Case 2: Disease Model for Childhood-Onset Dystrophinopathy

Characterize Covariates

- Retrieve RWD from MD StarNet (358 males born 1982-2011)
- Develop Disease Model (Time to loss of ambulation)
- Identify Prognostic Effect of Genetic Mutation

Joint effort from federal/state government & academia

Model Building

New Protocol Design
Identify Prognostic Effect of Genetic Mutation Disease Model with Covariate Effect

No Difference in Disease Progression by Genetic Mutation Type

Exon 8 and 44 Skippable Subgroups Showed Lower Risk of LoA Relative to Other Amenable Subgroups

Gregory Haber, Kristin M Conway, Pangaja Paramsothy, Anindya Roy, Hobart Rogers, Xiang Ling, Nicholas Kozauer, Natalie Street, Paul A Romitti, Deborah J Fox, Han C Phan, Dennis Matthews, Emma Ciafaloni, Joyce Oleszek, Katherine A James, Maureen Galindo, Nedra Whitehead, Nicholas Johnson, Russell J Butterfield, Shree Pandya, Swamy Venkatesh, Venkatesh Atul Bhattacharaj 

Improve Patient Enrichment, Randomization, and Matching
Duchenne Muscular Dystrophy

Matching Strategy

- Historical Control
- Trial

Using historical control subjects as a supplement to the placebo arm (Phase 2)

Randomization by Strata

- Placebo
- Treatment

Randomization by strata to ensure consistent disease progression in different arms.

Patient Enrichment

- Patient
- Trial

Enrich patients to reduce variability.
Case 3: Disease Model for Postmenopausal Osteoporosis

Link Short-Term Biomarker Changes
Identify Prognostic Effect of Genetic Mutation

Disease Model with Biomarkers

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Schematic Diagram for Disease-Drug Model

Various Biomarker Changes in Placebo and Treatment Arms

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Avenues for Regulatory Interaction
The Fit-for-Purpose (FFP) Initiative provides a pathway for regulatory acceptance of dynamic tools for use in drug development programs.

A designation of ‘fit-for-purpose’ (FFP) will be established based on a thorough evaluation of the information provided.

### Disease Area

<table>
<thead>
<tr>
<th>Disease Area</th>
<th>Submitter</th>
<th>Tool</th>
<th>Trial Component</th>
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</thead>
<tbody>
<tr>
<td>Alzheimer’s Disease</td>
<td>The Coalition Against Major Diseases (CAMD)</td>
<td>Disease model: Placebo/disease progression</td>
<td>Demographic &amp; drop out</td>
</tr>
<tr>
<td>Multiple</td>
<td>Janssen Pharmaceuticals &amp; Novartis Pharmaceuticals</td>
<td>Statistical model: MCP-Mod</td>
<td>Dose finding</td>
</tr>
</tbody>
</table>

Link to the FDA FPP initiative:
MIDD Paired Meeting Pilot Program

- This program is jointly administered by CDER and CBER.
- OCP is the point of contact.
- The sponsor should be a drug or a biologics developer.
- The product should be registered under an U.S. IND/NDA/BLA.
- FDA accepts requests on a continuous basis.
- FDA expects to grant 2-4 submissions on a quarterly basis.

Joint effort for:
1. all stake holders
2. multi-disciplinary review team members

Link to the FDA MIDD Program:
<https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program>
Complex Innovative Trial Design (CID) Program

- To support the goal of facilitating and advancing the use of complex adaptive, Bayesian, and other novel clinical trial designs.
- Meetings will be conducted by FDA’s CDER and CBER during fiscal years 2019 to 2022.
- Under the pilot meeting program, FDA will accept two primary meeting requests and two alternates per quarter.

The CID Pilot Meeting Program is designed to:

- Facilitate the use of CID approaches in late-stage drug development.
- Promote innovation by allowing FDA to publicly discuss the trial designs considered through the pilot meeting program, including trial designs for medical products that have not yet been approved by FDA.

Link to FDA CID Program:
<https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-pilot-meeting-program>
Collaboration Opportunities

**Academic Institutions**
- Collaborative Agreements (e.g., **MOU**, CRADA)
- CDER Network of Experts (NoE) Program

**Academic Faculty**
- Faculty Sabbatical/Scientific Visit Program
- Advisory Committees (AC)/Special Government Employee (SGE)

**Professional & Graduate Students**
- Doctor of Pharmacy APPE Rotations
- Clinical Pharmacology
- Pharmacy Student Experiential Program (PSEP)
- Student Summer Internships
- Professional and Graduate Students
- ORISE Fellows

**Industry, Non-Profit Organizations**
- IQ consortium
- Platform developers
Take Home Messages

• Disease-Drug-Trial Models are important tools for MIDD.
• This modeling approach is widely used to support new drug development.
• FPP, MIDD, and CID programs allow direct interactions between industry and FDA on various modeling approaches.
• We look forward to collaborations with all stakeholders to improve modeling tools that can be used to facilitate new drug development.
Acknowledgement

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- Dr. Maryanne Dingman
- DPM Members
- OCP Members
- Other Collaborators at FDA or Outside FDA
Reference to Disease Models from FDA


