Session II: Challenges and Solutions for Advancing DPM Uptake

Moderator: Raj Madabushi, Associate Director, Guidance and Scientific Policy, Office of Clinical Pharmacology, FDA
Welcome Back!

Session II Objectives:
- Explore barriers for advancing the use of disease progression modeling to aid in decision making
- Discuss essential needs to advance the use of disease progression modeling

Approach: Panel → Break Out Groups
- Panel focus: DPM Applications & Decision Making
- Break Out Group focus: Essentials to Advance DPM & Accountability
Panel: DPM Applications & Decision Making

Hao Zhu
FDA

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Dave Miller
Unlearn.Ai

Klaus Romero
Critical Path Institute

Moderator: Raj Madabushi, FDA, CTTI Project Team Lead
Use of Disease Progression Models to Support New Drug Development

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CTTI
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*Disclaimer: The views in this presentation are my personal and should not be construed as the official position of the US Food and Drug Administration.*
Outline

• Introduction
  – Disease Progression Models

• Disease Models at FDA and Case Examples
  – Disease Models at FDA
    (OCP’s Efforts and Examples of Disease Models)
  – Case Examples
    • Pediatric Extrapolation: Schizophrenia Disease-Drug-Trial Model

• General Considerations for Disease Progression Models

• Take Home Message
Quantitative Disease-Drug-Trial Models

Disease Model
- Natural Progression
- Biomarker vs. Outcome

Drug Model
- Exposure-Response for Efficacy & Safety

Trial Model
- Drop Out

Mechanistic Models

Semi-Mechanistic Models

Empirical Models

Disease Model Toolbox

History: 2020 Strategic Goals

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

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<thead>
<tr>
<th>No</th>
<th>Disease Model</th>
<th>Use</th>
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<tbody>
<tr>
<td>1</td>
<td>NSCLC Model [1]</td>
<td>Late Phase Trial Design.</td>
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<tr>
<td>2</td>
<td>Parkinson's Disease Model [2]</td>
<td>Endpoint Selection and Clinical Trial Design</td>
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<td>3</td>
<td>Alzheimer's Disease Model [3]</td>
<td>Endpoint Selection and Clinical Trial Design</td>
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<td>5</td>
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<td>7</td>
<td>HIV Model [4]</td>
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<td>Rheumatoid Arthritis Model [12]</td>
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<tr>
<td>14</td>
<td>Pulmonary Arterial Hypertension Model [13]</td>
<td>Endpoint Selection and Clinical Trial Design</td>
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Case Example: Disease Model for Schizophrenia
Characterize the Profile of the Disease Progression and ER

Retrieve Data from Submissions

Develop Disease-Drug Models in Adults

Predict Pediatric Disease Progression or Exposure-Response

Compare the Longitudinal Outcomes & Endpoints

Model Building

Internal & External Discussion

New Policy
Evidence to Demonstrate Disease Similarity and Response

Disease Model

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

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

General Considerations for Disease Modeling

• Modeling Objectives: (critical to determine subsequent actions)
• Data: (General principles for meta-analysis: source, information collected, endpoints, assay, study design, enrollment criteria, observational study vs. clinical trial, patient subgroups, handling of missing values, outliers, etc)
• Assumptions: (mathematical / statistical assumptions, biological assumptions, assumptions for information borrowing, etc)
  – Model Structure (e.g., linear vs. non-linear, current understanding of mechanism)
  – Covariate selection (e.g., missing covariates, imbalanced information from trials)
  – Parameters (e.g., borrowing information from different sources)
• Validation and verification (inline with the context of use, needed level of validation needs to be adjusted)
• Decision making (risk-based, factor in uncertainty)
• Reporting
Take Home Messages

• Disease-Drug-Trial Models are important tools for MIDD.

• FFP, MIDD, and CID programs allow direct interactions between industry and FDA on various modeling approaches.

• Several steps should be considered to ensure that the established disease model can be applied to support the targeted usage.
Acknowledgement

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- Dr. Issam Zineh
- DPM Members
- OCP Members
- Other Collaborators at FDA or Outside FDA
Applications of DPM: Attributes and Limitations – Sponsor perspective

C.J. Musante, VP & Global Head of QSP, Pfizer
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The presenter is an Employee of Pfizer Inc.
Quantitative Systems Pharmacology (QSP) Examples

DPM to Advance Decision Making Throughout the Medical Product Development Lifecycle
What is a QSP DPM?

... a modeling & simulation approach that mathematically describes the mechanistic relationships between target modulation and disease biomarkers & outcomes over time...

...to predict and interpret clinical responses to pharmacological intervention as part of a model informed drug development (MIDD) paradigm.

QSP DPM Applications in MIDD

Mechanistic Insight

Compound design & selection

Safety/tox Predictions

Trial design & simulation

Biomarkers & diagnostics

Comparative Efficacy

Target ID & evaluation

Preclinical study design

Translational predictions

Patient Stratification

Combination Strategies

Indication Evaluation

Different Examples - Common Themes

**QSP Model of the Immune Response to SARS-CoV-2**
- Preclinical to clinical translation
- Dose-response predictions
- Dose timing and treatment duration vs time of infection
- Comparative efficacy
- Efficacy predictions in different populations

**QSP Model of Non-Alcoholic Fatty Liver Disease (NAFLD)**
- Predicting combo efficacy in NAFLD based on healthy data for single agents
- Clinical trial simulations for single & combo arms in Ph 2 trial
  - Study duration
  - Doses
- Comparative efficacy

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Right: Rieger, T. “Development of virtual populations for prediction of the response to treatments for non-alcoholic fatty liver disease.” Presented at the 9th American Conference on Pharmacometrics, October 2019.
Key Common Themes

Each model

- was based on mechanistic understanding (at the time of development) of the target and disease
- was used to extrapolate to new conditions
- informed clinical trial design and accelerated the programs
- predictions were subsequently confirmed by trial results
Each model was based on mechanistic understanding \textit{(at the time of development)} of the target and disease.

Each model was used to extrapolate to new conditions.

Each model informed clinical trial design and accelerated the programs.

Predictions from each model were subsequently confirmed by trial results.

- However, the QSP NAFLD model initially mis-predicted a change in a key biomarker, resulting in a missed opportunity to address earlier in development.

What can we learn from these examples?
Two Examples: Compare & Contrast

**QSP Model of the Immune Response to SARS-CoV-2**

- Novel infectious disease of global concern
- Many biotech/pharma advancing vaccines & anti-virals, at unprecedented speed, several with EUA
- Clinical trial and real-world data rapidly emerging and submitted for peer-review publication and/or included in EUA submissions
- At the time of our clinical trial simulations, mAb and preliminary competitor anti-viral summary data were publicly available
- Relative confidence in mechanism of action, based on preclinical and clinical data

**QSP Model of Non-Alcoholic Fatty Liver Disease (NAFLD)**

- Under-studied/diagnosed disease with unmet need
- Highly competitive field with many agents in development; several fast-tracked
- Limited data available on disease progression in published literature; RWE lacking
- At the time of initial simulations, clinical data were not publicly available for this mechanism of action (MoA)
- Preclinical data did not translate to understanding the regulation of hepatic lipid metabolism in humans
- Once competitor data with same MoA were published, model was updated & successfully used to inform Phase 2
Summary: QSP DPMs

- Represent complex interactions *in time* between multiple drug targets, pathways, tissues, and organs/systems
- Mechanistically link target modulation to biomarker response &/or clinical outcomes
- Include untreated and treated patients and a range of disease phenotypes via virtual patients, populations, and trial simulations
- Allows for hypothesis testing & extrapolation beyond available data

“Success” largely dependent on confidence in the target and the mechanism(s) in the context of human disease
Acknowledgments

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- Brian Corrigan

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THANK YOU
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AI/ML: Value for DPM and Adoption Challenges

David P. Miller
Chief Science Officer, Unlearn.ai
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The presenter is an Employee of Unlearn.ai and owns equity in Unlearn.ai.
AI/ML → Deep Learning

- What is it?
- What is it good for?
- Why aren’t we already using it broadly today?
Deep Learning
What Is It?
Some folks still seem confused about what deep learning is. Here is a definition:

DL is constructing networks of parameterized functional modules & training them from examples using gradient-based optimization. facebook.com/722677142/post...

7:32 AM · Dec 24, 2019

Clear enough?
Can you tell the difference between a cat and a dog?
How do you know the cat is a cat?
Features and Parameters

Logistic Regression
What if pictures had more than cats and dogs?
AlexNet Ushered in a New Era of ML in 2012
Figure 2 from Krizhevsky, Sutskever, and Hinton
Deep Learning
What Is It Good For?
AI-generated Digital Twins provide a rich set of explanatory data for every participant in an RCT.
AI-Generated Digital Twins + Real Participants = Faster, Smaller Trials
CHMP qualifies PROCOVA
What are the key points in the qualification?

- Suitable for primary analysis of phase 3 pivotal studies
- Unbiased estimation of treatment effect
- Increased power
- Reduced sample size
The PROCOVA™ Procedure has 3 Steps

**Step 1**
“Training and evaluating a prognostic model to predict control outcomes”

**Step 2**
“Accounting for the prognostic model while estimating the sample size required for a prospective study”

**Step 3**
“Estimating the treatment effect from the completed study using a linear model while adjusting for the control outcomes predicted by the prognostic model”
Deep Learning
Why Aren’t We Already Using It Broadly Today?
Charles Fisher  
*Founder and CEO*

*Unlearn.AI*

*Unlearn is accelerating clinical trials with AI.*

"The biggest challenge in commercializing AI-based tech in healthcare is "the discernment problem" – most prospective customers can’t easily distinguish between companies using sophisticated AI and other companies selling nonsense as AI.

As a result, they assume you’re guilty until proven innocent. To overcome this, you need to do something big to stand out from the crowd.

In Unlearn's case, we've focused on paving the regulatory path and became the first company to receive a regulatory qualification for an AI-based approach to accelerating clinical trials. What can you do to show you're a cut above the rest?"
EMA vs FDA

- Submission April, 2021
- First meeting May, 2021
- Comments from EMA May, 2021
- Updated submission June, 2021
- EMA formal questions Sep, 2021
- Additional questions Dec, 2021
- Draft qualification Feb, 2022
- Public consult March, 2022
- Qualification Sep, 2022

- CPIM meeting March, 2020
- ISTAND submission June, 2021
- Eleven separate updates that there was no update (July, 2021 through June, 2022)
- Communication that there would be no more applications accepted in 2022 (July, 2022)
- Confirmation that ISTAND was the right path and there are no available resources to review (Dec 2022)
THANK YOU

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Disease Progression Modeling Without Tears

Transforming data into actionable knowledge for drug development

Klaus Romero MD MS FCP
Chief Science Officer
Critical questions for trial design

• How many patients should be recruited to properly power the trial?
• What should be the inclusion criteria?
• Can the control arm be optimized?
• What types of progression rates are expected for different subpopulations?
• What measures of progression are most adequate, at which stages of the disease continuum?
• How long should the trial duration be?
• How often should I assess?
• What is the time-varying probability of dropouts, and what are their predictors?

How should one go about providing sound quantitative answers to these questions?
Answer 1: Quantifying variability

Quantifying multiple sources of variability simultaneously within the patient population reduces overall unexplained variability

Result: The ability to predict more accurate progression rates for heterogeneous subpopulations of patients in clinical trials
Answer 2: Multiple data sources

Understanding the ‘universe’ of a given disease’s heterogeneity

Result: The ability to more accurately account for the heterogeneity in rare diseases and avoid biased conclusions on few data sources.
Answer 3: Drug-disease-trial modeling

- Disease progression and characterization model
- Disease modifying effect
- Placebo effects model, dropout model
- Drug effects model /
  Disease modifying effect

Longitudinal observational & clinical trial data
• Start with an understanding of what sponsors can practically use to design clinical trials, and reverse engineer

\[
S(t) = \frac{S_0}{S_0 + (1 - S_0^\beta) e^{-\beta t}}^{1/\beta}
\]

\[
TVP_i = \theta_i \left(\frac{\text{cont}_i}{\text{ref}}\right)^{\theta_{\text{power}}} \cdot \theta_{\text{cat}_i}^{\theta_{\text{coeff}}}
\]

\[
f(S; \alpha, \beta) = \frac{\Gamma(\alpha + \beta)}{\Gamma(\alpha) + \Gamma(\beta)} \cdot S^{(\alpha - 1)} \cdot (1 - S)^{(\beta - 1)}
\]
Total Data Contributed

Clinical Data
- Studies: 390
- Participants: 605,708

Non-Clinical Data
- Studies: 148
- Participants: 11,084

Note: Studies currently undergoing curation are only counted in Total Studies until evaluated.
Disease Progression Model

Input  Modeling  Output
Disease Progression Model

**Input**
Patient-level data

**Modeling**

**Output**
Disease Progression Model

**Input**
Patient-level data

**Modeling**
- Baseline severity
- Age
- Sex
- Demographics
- Genetics
- Medications
- Dropouts
- Baseline biomarkers
- Longitudinal biomarkers
- Longitudinal endpoints

**Output**
Disease Progression Model

Input

Clinical studies

Modeling

Output

Understanding of disease worsening
Trajectory Rate
Predictors
Web Clinical Trial Simulator

- Baseline severity
- Age
- Sex
- Genetics
- Medications
- Baseline biomarkers
- Longitudinal biomarkers
- Dropout
- Longitudinal endpoints
Disease Progression Model

Input | Modeling | Output

DATA | TRANSFORMATION | KNOWLEDGE
From data, to solutions, to impact

- **Alzheimer’s disease**
  - Solutions: 2 CTS tools, 2 biomarkers
  - Impact: First 2 disease-modifying drugs

- **Tuberculosis**
  - Solutions: Multiple quantitative tools
  - Impact: First new drug and drug regimen

- **PKD**
  - Solutions: PKD
  - Impact: First disease-modifying drug

- **Type 1 Diabetes**
  - Solutions: Model-based biomarkers
  - Impact: First prevention drug

- **Duchenne Muscular Dystrophy**
  - Solutions: 5 disease progression models
  - Impact: Transformed trial design paradigm

- **Kidney Transplantation**
  - Solutions: Composite biomarker endpoint
  - Impact: Transformed trial design paradigm

- **Parkinson’s disease**
  - Solutions: 3 CTS tools, 1 biomarker, multiple DHT solutions
  - Impact: Transformed trial design paradigm

- **Huntington’s disease**
  - Solutions: Staging system, 3 disease progression models
  - Impact: Transformed trial design paradigm
Thank you!