An Overview on Model Informed Drug Development (MIDD)

Hao Zhu, Ph.D., Mstat
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Outline

• MIDD:
  – Concept of MIDD:
  – History of Modeling and MIDD
  – Quantitative Models

• Value of MIDD
  – Policy Development
  – Dose Selection/Optimization
  – Evidence of Efficacy
  – Clinical Trial Design

• Current and Future Trends in MIDD

• Take Home Message
MIDD

• MIDD: Application of a broad range of quantitative models to facilitate drug development and decision making.

PK: Drug concentration change over time.
PD: Drug effect on body (efficacy and safety)
Disease: Disease progression over time
Variability: Difference among patients

Clinical Trial Simulation

Cell
Organ
Body
History of Quantitative Modeling

• MIDD has been built upon a century’s effort:
  – Pharmacokinetics model:
    • 1919: Widmark et al. Single-compartment open model for PK.
    • 1937: Teorell et al. Two-compartment model for PK
  – Pharmacodynamics model:
    • 1910: Hill et al. Hill equation (sigmoid Emax model) to describe the association between oxygen and hemoglobin
  – Population PK model:
    • 1972, Sheiner et al. Nonlinear mixed effects model to describe variability in PK.
  – Disease and clinical trial model:
    • 1992, Holford et al. Disease progression model for Alzheimer’s Disease.

Atkinson AJ Jr, Lalonde RL: [PMID: 17571065]
Learning versus confirming in clinical drug development

George Box views scientific progress as consisting of, and requiring, alternating steps of induction and deduction: the former being learning from experience, and the latter being confirmation of what has been learned. A simplified application of this view to clinical drug development, which I define to be first in humans to approval, would break development into two major learn-confirm cycles. In the first—phases I and 2A—one learns, in normal subjects, what dose is tolerated (phase I) and confirms that this dose has promise of efficacy in a selected group of patients (2A). The end of phase 2A is a decision point: Is there a sufficiently positive indication of efficacy (and lack of toxicity) to justify investing in the future development of the drug? If so, a larger and more costly learn-confirm cycle—phases 2B and 3—begins. The goal of the learning step of this cycle (2B) is to learn how to use the drug in modeling and simulation. Learn

Confirm

Phase 2

Phase 3

Concept of MIDD
Implementation of Models into Drug Development

Marshall 2016 [PMID 27069774]
Classification of Quantitative Models (1)

**Quantitative models:** Whether the models reflect the current understanding of mechanism.

- **Empirical model:** describes the shape.
- **Semi-mechanistic model:** Includes a simplified understanding of the process.
- **Mechanistic model:** Includes current understanding of the biological and pharmacological process.
Classification of Quantitative Models (2)

Determined by the utility of models
Value of MIDD

Dose optimization

Clinical trial design

Policy

Supportive evidence for efficacy

Wang 2019 [PMID 30653670]
Value of MIDD

2. New evidence source: Dose-response, exposure-response...
3. New policy for changes in new drug development in different disease areas

Wang 2019 [PMID 30653670]
FDA Published MIDD-related Guidance

- SUPAC Guidance
- ICH E 4 Guidance
- Population PK Guidance
- Exposure-response Guidance
- EOP 2 A Guidance
- ICH E14 (R3) Guidance
- Renal Impairment Guidance
- Hepatic Impairment Guidance
- Guidance for Acute Bacterial Skin Infection
- Guidance for HIV-1 Treatment
- Guidance for Pulmonary Tuberculosis
- Guidance for Clinical Pharmacology for Pediatric Studies
- Guidance for Animal Rules
- Guidance for Biosimilar
- PBPK format & Content Guidance
- Guidance for Extrapolation of Efficacy in Partial Onset Seizure
- Guidance for Antibacterial Therapies for Serious Bacterial Disease
- Guidance for HCV Infection
- Guidance for Prophylaxis of HIV1 Infection
- Guidance for Respiratory Syncytial Virus Infection
- Guidance for Pediatric Rare Disease
- Guidance for Single Enzyme Defects
- Guidance for In Vitro DDI
- Guidance for DDI
- Guidance for Hypertension
- Guidance for Ulcerative Colitis
- E17 Guidance
Policy: Extrapolation in Pediatric Partial Onset Seizure

- Efficacy extrapolation:
  - Basis for extrapolation
    - Similar progression of disease
    - Similar response of disease to treatment
    - Similar exposure-response relationship
  *: Quantitative models provide the basis for the demonstration of similar disease progression, similar response, and similar exposure-response relationship.
Efficacy back extrapolation:

- CNS Stimulant products (Methylphenidate and Amphetamine ER+IR formulation)
- PK profiles are consistent in patients with different age.

Basis for back extrapolation

- Efficacy is determined by PK profile
- Safety (e.g., blood pressure and heart rate) tracks PK profile.
Value of MIDD

1. Approval of new dosing regimens:
2. Deriving dosing regimens for subgroups of patients
3. Dose determination (e.g., animal rules)
4. Suggesting optimal dosing regimens post-approval:

Wang 2019 [PMID 30653670]
A long acting injectable antipsychotic indicated for the treatment of schizophrenia.

**Approval of New Dosing Regimens – Paliperidone LAI**

- **Slow Drug Release**
  - Ensures that concentration levels are maintained over a dosing interval of 4 weeks.
  - For a naïve patient, it takes 3-4 months before the concentration reaches the desirable range.
Approval of New Dosing Regimens – Paliperidone LAI

**Table:**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Initiation Dosing (deltoid)</th>
<th>Monthly Maintenance Dose* (deltoid or gluteal)</th>
<th>Maximum Monthly Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia (2.2)</td>
<td>234 mg, 156 mg</td>
<td>39-234 mg&lt;sup&gt;b&lt;/sup&gt;, 78-234 mg&lt;sup&gt;c&lt;/sup&gt;</td>
<td>234 mg</td>
</tr>
</tbody>
</table>

<sup>a</sup> Administered 5 weeks after the first injection.
<sup>b</sup> The recommended maintenance dose for treatment of schizophrenia is 117 mg. Some patients may benefit from lower or higher maintenance doses within the additional available strengths (39 mg, 78 mg, 156 mg, and 234 mg).
<sup>c</sup> Adjust dose based on tolerability and/or efficacy using available strengths. The 39 mg strength was not studied in the long-term schizoaffective disorder study.

* Labeled Loading dose:

Population PK Modeling and Simulation was performed to evaluate alternative dosing regimens.

1. A loading dose with two consecutive injections in one week has shown that the concentration will achieve the desirable range by the end of one week.
2. In combination with safety information from other trials.

The new loading dosing regimen has been approved without direct clinical assessment.
Extrapolation of Efficacy to Pediatrics - Humira

- Adalimumab (HUMIRA) is a recombinant human IgG1 monoclonal antibody that binds to human tumor necrosis factor-alpha (TNFα) is indicated for the treatment of Hidradenitis suppurativa (HS).

- HS is a rare disease in pediatric patients, where the prevalence is 0.002%, 0.027%, and 0.114% in patients < 9 years, 10-14 years, and 15-17 years.

- FDA expanded the dosing regimen to adolescent HS patients 12 years and older, weighing at least 30 kg without clinical trials.

Bi Y et al. PMID: 31325056
Pediatric Dose Determination – Humira

• Dosing regimen in patients > 12 years was determined through M&S relying on **PK-matching** with other patient populations (e.g. adults).

  – Pop-PK model with > 500 pediatric patients (other diseases) + > 3000 adults. Simulation was conducted to test alternative dosing regimens.

<table>
<thead>
<tr>
<th>Body Weight of Adolescent HS Patients (12 years and older)</th>
<th>Recommended Dosing regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 kg (66 lbs) to &lt; 60 kg (132 lbs)</td>
<td>• 80 mg initially on Day 1</td>
</tr>
<tr>
<td></td>
<td>• 40 mg on Day 8 and subsequent doses: 40 mg every other week</td>
</tr>
<tr>
<td>≥ 60 kg (132 lbs)</td>
<td>• 160 mg initially on Day 1; and</td>
</tr>
<tr>
<td></td>
<td>• 80 mg on Day 15</td>
</tr>
<tr>
<td></td>
<td>• 40 mg on Day 29 and subsequent doses: 40 mg every week</td>
</tr>
</tbody>
</table>
Deriving Dosing for Young Pediatrics

• Treatment of a life-threatening viral disease (public health emergency)

• Efficacy and Pharmacokinetic data from 200 adults
  – Age: 20-65 yrs; Weight: 40-110 Kg

• Target AUC established in adults

• Drug is cleared exclusively through renal route

Adopted from Dr. Qi Liu’s previous presentation
Allometry and Renal Function Maturation

Allometric model was used to fit data from adults

Renal function maturation was incorporated based on literature information

PK Prediction and Dose Selection in Young Pediatrics Patients

- Simulations combining renal function maturation and allometry allowed reasonable estimation of clearance in pediatric patients

- Simulations were conducted to select a dosing regimen
# Dose Determination

## Examples from Application of Animal Rule

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Approval Basis for Pediatric Use</th>
<th>Role of PK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raxibacumab</td>
<td>Treatment and prophylaxis of inhalational anthrax</td>
<td>Animal study + Extrapolation</td>
<td>M&amp;S to predict exposure in pediatric patients and to match exposure in adults receiving 40 mg/kg.</td>
</tr>
<tr>
<td>Tecovirimat</td>
<td>Treatment of human smallpox disease</td>
<td>Animal study + Extrapolation</td>
<td>M7S to predict exposure in pediatric patients and to match exposure in adults receiving 600 mg BID</td>
</tr>
</tbody>
</table>
Optimal dosing regimens – Vialzodone:

Indicated for the treatment of major depressive disorder
40 mg was the initially approved dose.

Package insert for Vialzodone.

Additional analysis showed a flat exposure-efficacy relationship and a steep exposure-safety relationship, suggesting lower dose may improve safety while maintaining efficacy.

Three clinical trials were submitted to support the initial approval of 40 mg dose.
Optimal dosing regimens – Vilazodone:

Indicated for the treatment of major depressive disorder
20 mg dose was added.

Package insert for Vilazodone.

Study 4 was conducted as a Post-marketing study showing that 20 mg dose is equally efficacious as compared to 40 mg with improved safety.
Value of MIDD

Wang 2019 [PMID 30653670]
# Efficacy Extrapolation in Pediatric Development

## Partial Onset Seizure in Pediatric Patients > 4 Years

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Approaches to Support Pediatric Indication</th>
<th>Role of PK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eslicarbazepine</td>
<td>Partial onset seizure in patients &gt; 4 years</td>
<td>Extrapolation</td>
<td>Bridging efficacy and deriving pediatric dosing</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Partial onset seizure in patients &gt; 4 years</td>
<td>Extrapolation</td>
<td>Bridging efficacy and deriving pediatric dosing</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Partial onset seizure in patients &gt; 4 years</td>
<td>Extrapolation</td>
<td>Bridging efficacy and deriving pediatric dosing</td>
</tr>
<tr>
<td>Brivaracetam</td>
<td>Partial onset seizure in patients &gt; 4 years</td>
<td>Extrapolation</td>
<td>Bridging efficacy and deriving pediatric dosing</td>
</tr>
</tbody>
</table>
Evidence of Efficacy

Boceprevir: For the treatment of chronic hepatitis C (CHC) genotype 1 infection.

Treatment-experienced patients were excluded from the initial clinical trials.

Model predicted similar treatment response in treatment-experienced patients.

Subsequent clinical trials.
Value of MIDD

Wang 2019 [PMID 30653670]
Schizophrenia Endpoint Optimization

• Current endpoint: Placebo-adjusted PANSS total score change from baseline at week 6 ~8.
• PANSS: (30 items), 30~60 minutes to administer.
  – Positive symptoms: 7 items
  – Negative symptoms: 7 items
  – General psychopathology symptoms: 16 items
Contribution from Different Items

**Item Response Theory**

- **P1**: Contributing Item
  - Probability of an option vs. Contributing Item

- **P5**: Non-contributing Item
  - Probability of an option vs. Non-contributing Item
Concordance between Week 4 and Week 6

Conclusion based on a 19-item PANSS total score collected at Week 4 is similar to that based on a 30-item PANSS total score collected at Week 6.
Current Trend: MIDD Paired Meeting Pilot Program

• Announced on April 16, 2018
• The MIDD Pilot Program is jointly administered by:
  – CDER’s Office of Clinical Pharmacology
  – CBER’s Office of Biostatistics and Epidemiology
• An opportunity for drug developers and FDA to discuss the application of MIDD approaches to the development and regulatory evaluation of medical products in development
• The goal is to provide advice on how specific, proposed MIDD approaches can be used in a specific drug development program
Process for MIDD Pilot Review Program

Madabushi R, PMID: 31081932
Public Workshops and Guidance Update

• Public Workshop
  – Oncology Dose Finding Workshop (2018)

• Guidance Update:
  – PBPK format and content guidance
  – Population PK guidance
  – Exposure-response guidance (FR notice)
Novel Technologies and Techniques

- Real World Data/Evidence:
  - Big Data: Electronic Health Record from daily practice.
  - Digital Biomarker: (e.g., iWatch, Wearables) Continuous data acquisition.
  - Digital Health: (Apps, Abilify Mycite)

- Pragmatic, decentralized clinical trials.
Novel Techniques and Technologies

- Mechanistic Models:
- AI/Machine Learning:

- Image date (CT or MRI Scan)
- Lab Measurement
- Clinical Assessment
- Other Patient Features
- ......
Take Home Message

• MIDD is an evolving concept: (Bring innovation into new drug development)
  – MIDD has been built upon a century’s exploration.
  – MIDD has been applied in various stages of clinical trial to:
    • Optimize dose selection
    • Improve clinical trial design
    • Identify the evidence for effectiveness
  – New techniques and technologies may bring new frontier for MIDD.
• MIDD is a regulatory tool: (facilitate early interaction between regulators and drug developers).
Acknowledgement

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Questions and Comments