Yaning Wang

• Director, Division of Pharmacometrics, Office of Clinical Pharmacology, US FDA (2017 – present)
• Acting Director, Division of Pharmacometrics, Office of Clinical Pharmacology, US FDA (2016 – 2017)
• Reviewer, Senior Reviewer, Team Leader, Associate Director, Deputy Director, Division of Pharmacometrics, Office of Clinical Pharmacology, US FDA (2003 – 2016)
• PhD in pharmaceutics and MS in statistics (2003)
• MS in biochemistry (1999)
• BS in pharmacy (1996)
Application of MIDD in New Drug Development and Approval

Yaning Wang, Ph.D.
Division of Pharmacometrics
Office of Clinical Pharmacology
OTS/CDER/OMTP/FDA
Application Overview

• Dose optimization
  – General population
  – Subgroups
  – Post-approval (PMR/PMC)

• Efficacy
  – Supportive evidence of effectiveness
  – Increased patient access

• Safety
  – Specific population

• Trial design
  – IND

• Policy change
  – QT/QTC interval prolongation and proarrhythmic risk
  – Extrapolation of anti-epilepsy drugs efficacy from adult to pediatric patients
Case 1: Paliperidone
Dose Optimization for General Population

• Indication: schizophrenia (monthly long acting injection formulation)
• Review issue: none of the studied regimens in phase 3 trials was optimal
  – All regimens were efficacious compared to placebo
  – One death at the highest dose and dose-dependent safety concerns
• Approach: population pharmacokinetic (PK) model and exposure-response model analyses
  – Target exposure: extended-release tablet (approved QD regimen)
• Outcome: an optimal regimen was derived and approved
  – PK simulations led to recommendations for dosing window, strategy for handling missing dose, switching from prior treatments, dosing regimen for special patients
Welcome to the Educational Dose Illustrator!

What Is the Educational Dose Illustrator?

The Educational Dose Illustrator can be used to visualize how dosing affects paliperidone plasma concentrations following administration of INVEGA SUSTENNA®. This resource simulates the paliperidone plasma concentrations over time resulting from different dosing scenarios that are set forth in the INVEGA SUSTENNA® Prescribing Information.
Missed 2nd Initiation Dose: >7 Weeks Since 1st injection

Typical Paliperidone Plasma Concentration (ng/mL)

234mg DelToid
234mg DelToid EDIT
117mg DelToid
117mg DelToid EDIT
117mg DelToid
117mg DelToid EDIT
117mg DelToid
117mg DelToid EDIT
156mg DelToid

INVEGA SUSTENNA® (paliperidone palmitate) is indicated for the treatment of:
- Schizophrenia in adults.
- Schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants in adults.

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS.
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA SUSTENNA® is not approved for use in patients with dementia-related psychosis.

https://www.educationaldoseillustrator.com/pp1m/schizophrenia
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Case 2: Edoxaban
Dose Optimization for Subgroups

• Indication: stroke and systemic embolism

• Review issue: different risk/benefit ratios in different subgroups
  – Post-hoc subgroup analyses showed patients with normal renal function could not
    achieve favorable risk/benefit even though both dose groups met NI margin relative to
    warfarin on efficacy, superior on major bleeding

• Approach: exposure-response model analyses (safety and efficacy)
  – In healthy subjects with normal renal function, renal clearance accounts for 60% of the
    total clearance of edoxaban
  – Low drug exposure in patients with normal renal function

• Outcome: different dose regimens were approved for patients with different
  renal functions
  – Do not use edoxaban in patients with CrCL > 95 mL/min
Phase 3 Results

Patients with Lower Exposures in the High Dose Edoxaban Appeared to do Better on Major Bleeds and Worse on Stroke/SEE Relative to Warfarin

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## Dose Optimization PMC/PMR

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>PMC/PMR</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ponatinib</td>
<td>Chronic myeloid leukemia</td>
<td>PMR</td>
<td>Lower dose</td>
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<tr>
<td>Vandetanib</td>
<td>Medullary thyroid cancer</td>
<td>PMR</td>
<td>Lower dose</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>Medullary thyroid cancer</td>
<td>PMR</td>
<td>Lower dose</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Ulcerative colitis</td>
<td>PMR</td>
<td>Higher dose</td>
</tr>
<tr>
<td>Mozobil</td>
<td>Mobilize hematopoietic stem cells</td>
<td>PMC</td>
<td>Higher dose in low body weight patients</td>
</tr>
<tr>
<td>Herceptin</td>
<td>GI cancer</td>
<td>PMR</td>
<td>Higher dose</td>
</tr>
<tr>
<td>Ado-trastuzumab emtansine</td>
<td>Metastatic breast cancer</td>
<td>PMC</td>
<td>Higher dose</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Melanoma</td>
<td>PMR</td>
<td>Higher dose</td>
</tr>
<tr>
<td>Omacetaxine mepesuccinate</td>
<td>Chronic myeloid leukemia</td>
<td>PMR</td>
<td>Higher dose</td>
</tr>
<tr>
<td>Radium Ra 223 dichloride</td>
<td>Prostate cancer</td>
<td>PMC</td>
<td>Higher dose</td>
</tr>
</tbody>
</table>
### Dose Optimization PMC/PMR

<table>
<thead>
<tr>
<th>Year approved</th>
<th>Drug name (brand name)</th>
<th>Indications</th>
<th>Approved highest maintenance dose in adults[^a]</th>
<th>Comments[^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>Gabapentin enacarbil (Horizant)</td>
<td>Restless legs syndrome (RLS)</td>
<td>600 mg</td>
<td>PMC: additional dose–response studies that include lower doses (300, 450 mg/day) are needed to define the maximally effective, lowest dose to relieve moderate to severe symptoms of RLS</td>
</tr>
<tr>
<td>2011</td>
<td>Vilazodone (Vibryd)</td>
<td>Major depressive disorder (MDD)</td>
<td>40 mg</td>
<td>PMC: some important adverse reactions are dose related; request to further characterize the efficacy and safety to evaluate 20- and 40-mg fixed doses in MDD</td>
</tr>
<tr>
<td>2010</td>
<td>Dalfampridine (Amryta)</td>
<td>Multiple sclerosis (MS)</td>
<td>10 mg twice daily</td>
<td>PMC: to evaluate the efficacy of 5-mg twice-daily dose in MS</td>
</tr>
<tr>
<td>2010</td>
<td>Cabazitaxel (Jevtana)</td>
<td>Hormone-refractory metastatic prostate cancer (mHRPC)</td>
<td>25 mg/m² every 3 weeks</td>
<td>PMC: to compare a lower dose (20 mg/m²) with 25 mg/m² in mHRPC</td>
</tr>
<tr>
<td>2010</td>
<td>Fingolimod (Gilenya)</td>
<td>Multiple sclerosis</td>
<td>0.5 mg daily</td>
<td>PMC: to evaluate a lower dose, 0.25 mg. The similarity in effectiveness of 0.5- and 1.25-mg doses suggests that a lower dose might be equally effective. The clinical findings of concern are clearly dose related</td>
</tr>
<tr>
<td>2010</td>
<td>Lurasidone (Latuda)</td>
<td>Schizophrenia</td>
<td>160 mg</td>
<td>PMC: to identify the lowest effective dose; to evaluate with a dose lower than 40 mg (e.g., 20 mg daily)</td>
</tr>
<tr>
<td>2009</td>
<td>Asenapine (Saphris)</td>
<td>Schizophrenia and bipolar mania</td>
<td>10 mg twice daily</td>
<td>PMC: to identify the lowest effective dose; to study a dose &lt;10 mg twice daily (e.g., 5 mg twice daily) in bipolar mania and to study a dose &lt;5 mg twice daily (e.g., 2.5 mg twice daily) in schizophrenia</td>
</tr>
<tr>
<td>2008</td>
<td>Rilonacept (Arcalyst)</td>
<td>Cryopyrin-associated periodic syndrome</td>
<td>160 mg weekly</td>
<td>PMC: to assess whether either lower maintenance doses or a longer interval between doses could be equally effective but potentially safer than the approved dose</td>
</tr>
<tr>
<td>2008</td>
<td>Desvenlafaxine (Pristiq)</td>
<td>MDD</td>
<td>50 mg</td>
<td>PMC: to evaluate efficacy at 10, 25, and 50 mg/day. The available data suggest a flat dose–response curve for efficacy between 50 and 400 mg/day. There is a clear dose response for adverse events as the dose increases from 50 to 400 mg/day</td>
</tr>
<tr>
<td>2006</td>
<td>Paliperidone (Invega)</td>
<td>Schizophrenia</td>
<td>12 mg</td>
<td>PMC: to conduct a study to explore for a minimal effective dose</td>
</tr>
</tbody>
</table>

[^a]: mg, mg/m²

[^b]: CMS: Centers for Medicare & Medicaid Services
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Case 3: Everolimus
Supportive evidence of effectiveness

• Indication: prevention of rejection in liver transplantation
• Review issue: unique trial design for ethical reasons made it impossible to calculate non-inferiority (NI) margin based on methods recommended in the FDA NI guidance
• Approach: an innovative model-based exposure-response method was applied to derive a conservative NI margin based on the control arm data from the phase 3 trial
• Outcome: totality of evidence was applied to reach the final approval decision
Publications

Justification of Noninferiority Margin: Methodology Considerations in an Exposure–Response Analysis

Y Wang¹, Y Harigaya², M Cavaillé-Coll³, P Colangelo² and KS Reynolds²

Estimating the Contribution of Everolimus to Immunosuppressive Efficacy When Combined With Tacrolimus in Liver Transplantation: A Model-Based Approach

T Dumortier¹, M Looby¹, O Luttringer¹, G Heimann², J Klupp³, G Junge³, S Witte¹, R VanValen⁴ and D Stanski⁵

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 97 NUMBER 4 | APRIL 2015
CDE文章||定量药理学在确定非劣效试验界值中的作用

Role of pharmacometrics in defining the non-inferiority margin

作者

王玉珠，杨进波 Office of Statistics and Clinical Pharmacology

国家食品药品监督管理总局 药品审评中心 Center for Drug Evaluation of NMPA

http://www.sohu.com/a/223806858_324204
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Case 4: Boceprevir and Telaprevir
Efficacy: Increased Patient Access

• Indication: HCV
• Review issue: given the convincing efficacy results of both drugs in the treatment-naïve HCV patients, can the drugs be approved in experienced patients (one subgroup not studied)?
• Approach: bridging pharmacometric analyses
  – No resistance to peginterferon/ribavirin
• Outcome: regimens were approved for all patients
  – Shorter regimen was approved for one subgroup
April 29, 2011 — Boceprevir (VICTRELIS, Merck) received unanimous approval from participants in the Antiviral Drugs Advisory Committee meeting, who voted 18 to 0 that it should receive US Food and Drug Administration (FDA) approval for the treatment of chronic hepatitis C virus (HCV) infection.

On the first day of the meeting, held April 27 and 28, panelists considered the efficacy and safety data for boceprevir, which, if approved, will be administered at a dose of 800 mg 3 times a day, every 7 to 9 hours, with food. Boceprevir will be indicated for the treatment of patients with chronic HCV genotype 1 infection in combination with current standard therapy.

April 29, 2011 — Following in the wake of a unanimous vote for boceprevir yesterday, telaprevir (Vertex Pharmaceuticals, Inc) also received unanimous approval from the Antiviral Drugs Advisory Committee panelists, who voted 18 to 0 that the novel protease inhibitor should receive US Food and Drug Administration (FDA) approval for the treatment of chronic hepatitis C virus (HCV) infection.

The panel voted yes to the question of whether the available data support approval of the telaprevir in combination with other HCV drugs, pegylated interferon and ribavirin. The FDA is expected to make a decision on the approval of telaprevir by May 23, 2011.
Publications and Praise from Experts

**HEPATATOLOGY**

Response-guided telaprevir therapy in prior relapers? The role of bridging data from treatment-naive and experienced subjects玻璃

Jiang Liu, Pravin R. Jadhav, Shashi Amur, Russell Fleischer, Thomas Hammerstrom, Linda Lewis, Lisa Naeger, Julie O’Rear, Michael Pacanowski, Sarah Robertson, Shirley Seo, Greg Soon, Debra Birnkrant... See fewer authors

First published: 06 April 2012 | [https://doi.org/10.1002/hep.25764](https://doi.org/10.1002/hep.25764) | Citations: 13

**HEPATATOLOGY**

Boceprevir dosing for late responders and null responders: The role of bridging data between treatment-naïve and -experienced subjects玻璃

Jeffry Florian玻璃, Pravin R. Jadhav, Shashi Amur, Ruben Ayala, Patrick Harrington, Poonam Mishra, Jules O’Rear, Michael Pacanowski, Sarah Robertson, Mary Singer, Greg Soon, Wen Zeng, Jeffrey Murray


**HEPATATOLOGY**

The FDA, bridging data, and hepatitis C玻璃

Michael W. Fried M.D., Donald M. Jensen M.D.

First published: 29 November 2012 | [https://doi.org/10.1002/hep.26177](https://doi.org/10.1002/hep.26177) | Citations: 1

“However, neither scholars nor soothsayers alike would have accurately predicted the final labeling recommendations that accompanied the approval by the U.S. Food and Drug Administration (FDA).”

“The logic and elegant analyses encompassing CDER regulatory science and AIMS are evident in the current articles that synthesize (or “bridge”) data from multiple datasets provided to them by pharmaceutical sponsors (Merck and Vertex, in this case), made several assumptions, weighed risks and benefits, and then developed modified treatment algorithms that do not completely mirror those regimens studied in phase III trials.” These analyses have far-ranging implications for patients, clinicians, and for clinical investigators.”
## Many More Examples

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clevidipine</td>
<td>Acute hypertension</td>
</tr>
<tr>
<td>Paricalcitrol</td>
<td>Hyperthyroidism associated with chronic renal failure</td>
</tr>
<tr>
<td>Paliperidone ER</td>
<td>Adolescent Schizophrenia</td>
</tr>
<tr>
<td>Mirabegron</td>
<td>over-reactive bladder</td>
</tr>
<tr>
<td>Pralidoxime</td>
<td>Chemical poisonings for peds</td>
</tr>
<tr>
<td>Zosyn</td>
<td>Intra-abdominal infections</td>
</tr>
<tr>
<td>Trileptal</td>
<td>seizure</td>
</tr>
<tr>
<td>Topomax</td>
<td>seizure</td>
</tr>
<tr>
<td>Busulfan</td>
<td>chronic myelogenous leukemia</td>
</tr>
<tr>
<td>Canakinumab</td>
<td>Cryopyrin-Associated Periodic Syndromes</td>
</tr>
<tr>
<td>Raxibacumab</td>
<td>Inhalational Anthrax</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>HCV</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>HCV</td>
</tr>
<tr>
<td>Danuravir</td>
<td>HIV</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>severe allergic reactions</td>
</tr>
<tr>
<td>Nexium IV</td>
<td>GERD patients with a history of erosive esophagitis</td>
</tr>
<tr>
<td>Levocetrizine</td>
<td>allergic rhinitis</td>
</tr>
<tr>
<td>Danuravir</td>
<td>HIV</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>HCV</td>
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<td>Dapagliflozin</td>
<td>Diabetes</td>
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<tr>
<td>Drug</td>
<td>Specific question(s) addressed using PBPK</td>
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<tr>
<td>Diltiazem</td>
<td>Interaction of diltiazem with simvastatin</td>
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<tr>
<td>Ponatinib</td>
<td>Effect of a strong CYP3A inducer (rifampin) on ponatinib exposure</td>
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<tr>
<td>Rivaroxaban</td>
<td>Assessing a complex and multiple interaction scenario: subjects with renal impairment and coadministered a combined P-gp and CYP3A4 inhibitor (weak or moderate)</td>
</tr>
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<tr>
<td>Macitentan</td>
<td>Effect of a strong CYP3A inhibitor on macitentan steady-state exposure</td>
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<tr>
<td>Ibrutinib</td>
<td>Effect of a moderate CYP3A inducer or inhibitor on ibrutinib exposure</td>
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<tr>
<td>Simeprevir</td>
<td>Assessing the significance of a transporter (OATP1B1/3) on simeprevir disposition</td>
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Case 5: Obeticholic Acid (OCA)  
Safety in Specific Population

- Indication: primary biliary cholangitis (PBC)
- Review issue: given the increased plasma exposure level for patients with hepatic impairment, should the dose be reduced?
  - Based on physiologically based pharmacokinetic modeling (PBPK) predictions of liver (tissue) concentration, the applicant suggested no dose adjustment for patients with hepatic impairment
- Approach: exposure-safety analyses
  - Uncertainty of the relevance of tissue concentration for multiple safety endpoints
- Outcome: a reduced dose was approved for this specific subgroup
FDA Drug Safety Communication: FDA warns about serious liver injury with Ocaliva (obeticholic acid) for rare chronic liver disease

Safety Announcement

[09-21-2017] The Food and Drug Administration (FDA) is warning that the liver disease medicine Ocaliva (obeticholic acid) is being incorrectly dosed in some patients with moderate to severe decreases in liver function, resulting in an increased risk of serious liver injury and death. These patients are receiving excessive dosing, particularly a higher frequency of dosing than is recommended in the drug label for them. Ocaliva may also be associated with liver injury in some patients with mild disease who are receiving the correct dose. The recommended dosing and monitoring for patients on Ocaliva are described in the current drug label. We are working with the drug manufacturer, Intercept Pharmaceuticals, to address these safety concerns.

Ocaliva is used to treat a rare, chronic liver disease known as primary biliary cholangitis (PBC). PBC causes the bile ducts in the liver to become inflamed, damaged and destroyed. This causes bile, a fluid that helps in digestion, to build up in the liver. This build-up damages the liver over time, eventually causing it to lose its ability to function. Ocaliva has been shown to improve a certain blood test that measures liver problems.

Health care professionals should determine the patient’s baseline liver function prior to starting Ocaliva. Patients with moderate to severe liver impairment (Child-Pugh B and C) should be started on the approved dosing schedule of 5 mg once weekly, rather than the 5 mg daily dosing used for other PBC patients, and if

https://www.fda.gov/Drugs/DrugSafety/ucm576656.htm
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Case 6: Compound X
IND Trial Design

• Proposed indication: type 2 diabetes mellitus
• Review issue: polymorphism in metabolic enzyme and large variability in drug exposure among patients leading to different responses (efficacy and safety)
  – how to manage a genotypic influence on drug clearance in dose selection for Phase III trial design
• Approach: dose-exposure-biomarker-surrogate models
  – Data from other compounds were leveraged
  – Clinical trial simulation (in silico clinical trials)
• Outcome: recommendations related to dose levels, dosing frequency, time to select phase 3 dosing regimen and trial design
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Case 7: Evolution of Concentration-QTc Analysis

- QT/QTc prolongation risk should be thoroughly assessed for all new molecular entities
- Guidance: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarhythmic Drugs
- Analysis methods
  - Intersection union test (E14 primary before December 2015)
  - Concentration-QTc analysis (E14 supportive or primary after December, 2015)
- Dedicated thorough QT study (TQT) versus typical phase 1 studies
Evidence to Support ICH E14 Updates

• More than 10 years experience of concentration-QTc analysis
  – Good concordance between concentration-QTc and central tendency analysis

• IQ-CSRC prospective study
  – Successfully characterized the QTc effect based on concentration-QTc analyses for 5 ‘QT-positive’, 1 QT negative well known drugs

• Concentration-QTc analyses for data subsampled from TQT studies

• PK/PD simulation to evaluate effects of study design, sample size, dose range, ECG variability on concentration-QTc analyses
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Case 8: Extrapolation of Anti-Epilepsy Drugs (AED) Efficacy from Adult to Pediatric Patients

• Collaboration among Pediatric Epilepsy Academic Consortium on Extrapolation (PEACE), University of Maryland and FDA
• Efforts to make pediatric drug development more efficient
• Full extrapolation already applied for monotherapy of partial onset seizures (POS)
• To support full extrapolation for adjunctive therapy of POS
  – Analysis of existing data (7 drugs) to demonstrate similar exposure-response relationship between adult and pediatric patients
New Policy

• Division of Neurology Products has determined that it is acceptable to extrapolate to pediatric patients 4 years of age and older the effectiveness of drugs approved for the treatment of partial onset seizures (POS) in adults.

• Required information to support an indication for the treatment of POS in patients 4 years and older that relies upon extrapolation:
  – Approved indication for the treatment of POS in adults.
  – A pharmacokinetic analysis to determine a dosing regimen that provides similar drug exposure (at levels demonstrated to be effective in adults) in pediatric patients 4 years of age and older and in adult patients with POS. This analysis will require pharmacokinetic data from both the adult and pediatric (4 years of age and older) populations.
  – Long-term open-label safety study(ies) in pediatric patients 4 years of age and older.
“Systematic and quantitative analyses conducted by FDA, using data from clinical studies of drugs approved for the treatment of POS in both adults and pediatric patients, have shown that the relationship between exposure and response (reduction in seizure frequency) is similar in adults and pediatric patients 4 years of age and older. These drugs have a variety of putative mechanisms of action. These analyses and observations have allowed FDA to conclude that the efficacy of drugs approved for the treatment of POS can be extrapolated from adults to pediatric patients 2 years of age and older.”

“Simulations should be performed to select doses expected to achieve exposures similar to those in adults. The sample size and sampling scheme should be planned carefully to enable characterization of pharmacokinetics with adequate precision⁴. Pharmacokinetic data from that study should be used to determine pediatric dose and regimens that provide drug exposure similar to that known to be effective in adult patients with POS.”

Next Disease Areas

• Schizophrenia and Bipolar I Disorder

• Historically, one or more adequate and well-controlled clinical studies are required to demonstrate efficacy in pediatric patients with schizophrenia (> 13 years) or bipolar I disorder (> 10 years)

Assessment of Similarity in Antipsychotic Exposure-Response Relationships in Clinical Trials Between Adults and Adolescents With Acute Exacerbation of Schizophrenia

Shamir N Kalaria 1, Tiffany R Farchione 2, Mitchell V Mathis 2, Mathangi Gopalakrishnan 1, Islam Younis 2, Ramana Uppoor 3, Mehul Mehta 3, Yaning Wang 3, Hao Zhu 3

Affiliations + expand
PMID: 31994186 DOI: 10.1002/jcph.1580
Advancing Model-Informed Drug Development
PDUFA VI

• FDA will develop its regulatory science and review expertise and capacity in MIDD approaches. This staff will support the highly-specialized evaluation of model-based strategies and development efforts.

• FDA will convene a series of workshops to identify best practices for MIDD.
  – Physiologically-based pharmacokinetic modeling
  – Design analysis and inferences from dose-exposure-response studies
  – Disease progression model development, including natural history and trial simulation
  – Immunogenicity and correlates of protection for evaluating biological products, including vaccines and blood products

• Starting in FY 2018, FDA will conduct a pilot program for MIDD approaches. These meetings will be led by the clinical pharmacology or biostatistical review components within CDER or CBER.
  – FDA will select 2-4 proposals (e.g., 1-2 per Center) quarterly each year
  – Evaluate dosing, duration, and patient selection in a way that can inform regulatory decision-making

• By end of FY 2019, FDA will publish draft guidance, or revise relevant existing guidance, on model-informed drug development. By end of FY 2021, 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.

MIDD Pilot Meeting Process

## MIDD Submissions to FDA 1st PDUFA VI Year

### Table 1. The US Food and Drug Administration's model-informed drug development Paired Meeting Pilot Program: first-year submissions

<table>
<thead>
<tr>
<th>Quarter (start month)</th>
<th>Meeting requests (granted/denied), n</th>
<th>Drug development phase</th>
<th>Therapeutic area</th>
<th>MIDD topic</th>
<th>MIDD methods</th>
<th>Sponsor meetings, n⁰</th>
<th>Internal meetings, n⁰</th>
<th>Regulatory impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Quarter (July 2018)</td>
<td>3 (2/1)</td>
<td>Postapproval</td>
<td>Cardiovascular; oncology</td>
<td>Dose/dosing; clinical trial simulation</td>
<td>POPPK; POPPK/PD</td>
<td>4</td>
<td>8</td>
<td>Aligned on regulatory pathway for seeking new dosing for labeling without additional clinical dosing, efficacy, or safety studies</td>
</tr>
<tr>
<td>2nd Quarter (October 2018)</td>
<td>4 (4/0)</td>
<td>Phase I/II, phase II, phase IIb/III</td>
<td>Dermatology; infectious disease; neurology; rheumatology</td>
<td>Dose/dosing; clinical trial simulation</td>
<td>POPPK; D-R; E-R; Bayesian E-R; semimechanistic PK/PD</td>
<td>6⁰</td>
<td>14</td>
<td>Aligned on use of translational and clinical PK/PD strategies for dose selection in phase II/III or dose optimization after phase III</td>
</tr>
<tr>
<td>3rd Quarter (January 2019)</td>
<td>5 (4/1)</td>
<td>Preclinical, phase I/ Ib, phase II, postapproval</td>
<td>Cardiovascular; hematology; oncology</td>
<td>Dose/dosing; clinical trial simulation; mechanistic safety</td>
<td>POPPK; drug-disease-trial model; systems biology, QSP</td>
<td>8</td>
<td>17</td>
<td>Aligned on model validation and use of in silico clinical trial approaches for patient/dose selection; alignment with MIDD-informed paradigm for new formulation development</td>
</tr>
<tr>
<td>4th Quarter (April 2019)</td>
<td>3 (3/0)</td>
<td>Phase II, postapproval</td>
<td>Hematology; oncology</td>
<td>Dose/dosing; clinical trial simulation</td>
<td>POPPK; E-R; semimechanistic PK/PD</td>
<td>6</td>
<td>12</td>
<td>To be evaluated</td>
</tr>
<tr>
<td>Total</td>
<td>15 (13/2)</td>
<td>Preclinical to postapproval</td>
<td>7</td>
<td>All priority topics</td>
<td>Well established to emerging methodologies</td>
<td>24</td>
<td>51</td>
<td></td>
</tr>
</tbody>
</table>

This table provides a summary of the US Food and Drug Administration's (FDA's) model-informed drug development (MIDD) Paired Meeting Pilot Program experience for each quarter since its launch. The information is summarized by drug development phase, therapeutic area, specific MIDD application, methods applied, meeting numbers, and regulatory impact. D-R, dose–response; E-R, exposure–response; PK/PD, pharmacokinetics/pharmacodynamics; POPPK, population pharmacokinetics; POPPK/PD, population pharmacokinetics/pharmacodynamics; QSP, quantitative systems pharmacology. a: Includes meetings that were conducted, scheduled, or to be scheduled. b: Upon sponsor request, two follow-up meetings with the FDA were cancelled, as the objectives of the meetings were deemed to be fulfilled by previous interactions; additionally, two sponsors requested delaying the follow-up meeting (see text for details).
Therapeutic Areas

Total: 37
# Drug Development Phase

<table>
<thead>
<tr>
<th>Clinical Phase</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical/FIH, Phase I</td>
<td>4</td>
</tr>
<tr>
<td>Phase 1, Phase 2</td>
<td>1</td>
</tr>
<tr>
<td>Phase 2</td>
<td>7</td>
</tr>
<tr>
<td>Phase 2, Phase 3</td>
<td>9</td>
</tr>
<tr>
<td>Phase 3</td>
<td>6</td>
</tr>
<tr>
<td>Phase 3, Post-approval</td>
<td>3</td>
</tr>
<tr>
<td>Post-approval</td>
<td>7</td>
</tr>
</tbody>
</table>
## MIDD Applications

<table>
<thead>
<tr>
<th>MIDD Application</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial simulation/clinical trial design</td>
<td>2</td>
</tr>
<tr>
<td>Clinical trial simulation/clinical trial design, Supportive evidence of efficacy</td>
<td>1</td>
</tr>
<tr>
<td>Dose selection/optimization</td>
<td>9</td>
</tr>
<tr>
<td>Dose selection/optimization, Clinical trial simulation/clinical trial design</td>
<td>20</td>
</tr>
<tr>
<td>Dose selection/optimization, Clinical trial simulation/clinical trial design, Supportive evidence of efficacy</td>
<td>1</td>
</tr>
<tr>
<td>Dose selection/optimization, Predictive or mechanistic safety</td>
<td>1</td>
</tr>
<tr>
<td>Dose selection/optimization, Predictive or mechanistic safety, Clinical trial simulation/clinical trial design</td>
<td>1</td>
</tr>
<tr>
<td>Dose selection/optimization, Supportive evidence of efficacy</td>
<td>1</td>
</tr>
<tr>
<td>Predictive or mechanistic safety, Dose selection/optimization, Clinical trial simulation/clinical trial design, Supportive evidence of efficacy</td>
<td>1</td>
</tr>
</tbody>
</table>
# Quantitative Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-disease-trial, Population Pharmacokinetic, Semi-mechanistic PK/PD</td>
<td>1</td>
</tr>
<tr>
<td>Drug-disease-trial, Semi-mechanistic PK/PD, Population Pharmacokinetic</td>
<td>1</td>
</tr>
<tr>
<td>Exposure-Response</td>
<td>3</td>
</tr>
<tr>
<td>Exposure-Response, Dose-response</td>
<td>1</td>
</tr>
<tr>
<td>Exposure-Response, Dose-response, Population Pharmacokinetic</td>
<td>1</td>
</tr>
<tr>
<td>Exposure-Response, Population Pharmacokinetic</td>
<td>12</td>
</tr>
<tr>
<td>Exposure-Response, Population Pharmacokinetic, Drug-disease-trial, Semi-mechanistic PK/PD</td>
<td>1</td>
</tr>
<tr>
<td>Exposure-Response, Semi-mechanistic PK/PD</td>
<td>1</td>
</tr>
<tr>
<td>Model-based-meta-analyses</td>
<td>1</td>
</tr>
<tr>
<td>Physiologically Based Pharmacokinetic</td>
<td>1</td>
</tr>
<tr>
<td>Population Pharmacokinetic</td>
<td>3</td>
</tr>
<tr>
<td>Quantitative Systems Pharmacology</td>
<td>2</td>
</tr>
<tr>
<td>Quantitative Systems Pharmacology, Drug-disease-trial</td>
<td>3</td>
</tr>
<tr>
<td>Semi-mechanistic PK/PD</td>
<td>5</td>
</tr>
<tr>
<td>Semi-mechanistic PK/PD, Drug-disease-trial</td>
<td>1</td>
</tr>
</tbody>
</table>
Regulatory Impact

- Aligned on a regulatory pathway without further clinical studies
- Agreed on endpoints for use in trials
- Aligned on labeling language
- Aligned on MIDD approach/strategy
- Aligned on trial dose selection and design
- Alleviated the need for additional studies (i.e., fewer studies needed)
- Smaller study needed (i.e., fewer treatment arms or fewer patients)
Two Completed Cases

• Sotalol and Ramucirumab

  – MIDD meetings: discuss the model-based strategy to add a new dosing regimen to the product label

  – sNDA/sBLA: detailed in silico trials were submitted for review

  – Outcome: a new dosing regimen (shorter hospital stay for sotalol and shorter infusion time for ramucirumab) was added to the label based on the evidence from the in silico trials

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022306s005lblrpl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125477s036lbl.pdf
• “In Silico clinical trials use computer models and simulations to develop and assess devices and drugs, including their potential risk to the public, before being tested in live clinical trials.”

• “In Silico trials may potentially protect public health, advance personalized treatment, and be executed quickly and for a fraction of the cost of a full scale live trial.”

• “The FDA has advocated the use of such systems as an additional innovative research tool.”

• “Therefore, the Committee urges FDA to engage with device and drug sponsors to explore greater use, where appropriate, of In Silico trials for advancing new devices and drug therapy applications.

https://www.govinfo.gov/content/pkg/CRPT-114srpt82/pdf/CRPT-114srpt82.pdf
FDA-Wide Initiatives

Modeling Initiatives at FDA Centers

3-in-5 format (three slides in 5 mins)

- Specific strategic priorities for your Center around M&S
- What has changed in the last 5 years?
- What do you anticipate in the next 5 years?

- CBER: Richard Forshee
- CDER: Yaning Wang
- CDRH: Tina Morrison
- CFSAN: Jane van Dorn
- CTP: Kausar Riaz Ahmed
- CVM: Marilyn Martinez
- NCTR: Huixiao Hong
- ORA: Tomas Drgon

Recordings: https://collaboration.fda.gov/p81lvh7qzth/; https://collaboration.fda.gov/p8nxta18f86/; https://collaboration.fda.gov/p3pn29t4jip/
2021 New Alternative Methodologies

A Message from the FDA Commissioner

- I am proud to highlight in this report some of the activities in which FDA is engaged that are moving us closer to the goal of replacing, reducing, and refining the use of animals in medical product development while continuing to advance disease modeling, toxicology, and pharmacology in support of FDA’s mission.

https://www.fda.gov/media/144891/download
2021 New Alternative Methodologies

• **Center for Tobacco Products**
  – FDA’s Center for Tobacco Products (CTP) has pursued several applied research projects using in vitro and *in silico* techniques to broaden our understanding of toxicities from tobacco products.
  – CTP encourages the use of alternative methods for testing toxicity when it is appropriate and has sought to use in vitro and in silico methods synergistically...

• **Center for Devices and Radiological Health**
  – In 2019, the Center for Devices and Radiological Health (CDRH) continued to successfully deliver several *in vitro* and *in silico* methods to predict and assess health risks from exposure to medical device extractables and leachables.

• **Center for Veterinary Medicine**
  – Currently, through an understanding of drug physicochemical properties, formulation-critical quality attributes, and, in some cases, the use of physiologically based pharmacokinetic (*in silico*) models, the Center for Veterinary Medicine (CVM) is developing roadmaps for alternative approaches for the BE evaluation of these various types of products.

• **The Alternative Methods Working Group (formed in 2019)**
  – The Working Group seeks opportunities to advance innovative technologies and tools as well as new and potential applications of alternative systems (*in vitro*, *in vivo*, *in silico*, and systems toxicology modeling) that offer alternative methods to traditional toxicity and efficacy testing across FDA’s product areas.

[https://www.fda.gov/media/144891/download](https://www.fda.gov/media/144891/download)
Global Regulatory Harmonization

- US FDA: Divisions/working groups across all centers
- Europe: EMA modeling and simulation group
- Japan: PMDA modeling and simulation group
- Canada: HC modeling and simulation working group
- China: NMPA office of statistics and clinical pharmacology
  - NMPA already published its MIDD guidance in 2020
- Ongoing ICH discussion to create ICH MIDD guideline
- Quarterly international cluster meeting for pharmacometrics (FDA, EMA, PMDA, HC, TGA)
MIDD: Current and Future

Model-Informed Drug Development: Current US Regulatory Practice and Future Considerations

Yaning Wang¹, Hao Zhu¹, Rajanikanth Madabushi¹, Qi Liu¹, Shiew-Mei Huang¹ and Issam Zineh¹

¹Office of Clinical Pharmacology, Office of Translational Sciences, US Food and Drug Administration, Silver Spring, Maryland, USA.

*Correspondence: Yaning Wang (Yaning.Wang@fda.hhs.gov)

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Future:
• MIDD pilot
• Mechanistic models
• Machine-learning models
• Real-world data/real-world evidence
Summary

• Models with different levels of complexities have been applied to make decisions in drug development and regulatory review.

• Model Informed Drug Development (MIDD) activities under PDUFA VI and multiple initiatives provide additional momentum to apply in silico methods in more areas.

• Global acceptance is expected with a harmonized guideline.
Acknowledgments

- Division of Pharmacometrics
- Office of Clinical Pharmacology
- Office of Biostatistics
- Office of New Drug
- Colleagues from EMA, HC, NMPA, PMDA, TGA
- Many sponsors
THANK YOU