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)

FDA U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

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
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  - IND
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  - 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

Prescribing Information for: INVEGA® (paliperidone) | INVEGA SUSTENNA® (paliperidone palmitate) | INVEGA TRINZA® (paliperidone palmitate)

Educational Dose Illustrator

INVEGA SUSTENNA® (paliperidone palmitate) For Schizophrenia

INVEGA SUSTENNA® (paliperidone palmitate) For Schizoaffective Disorder

INVEGA TRINZA® (paliperidone palmitate) For Schizophrenia

Home | Starting a Patient on INVEGA SUSTENNA® | Switching a Patient to INVEGA SUSTENNA® | Managing a Missed Dose | Single Dose Curve View | Read More About INVEGA SUSTENNA®

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.

INVEGA® (paliperidone) | INVEGA SUSTENNA® (paliperidone palmitate) | INVEGA TRINZA® (paliperidone palmitate)

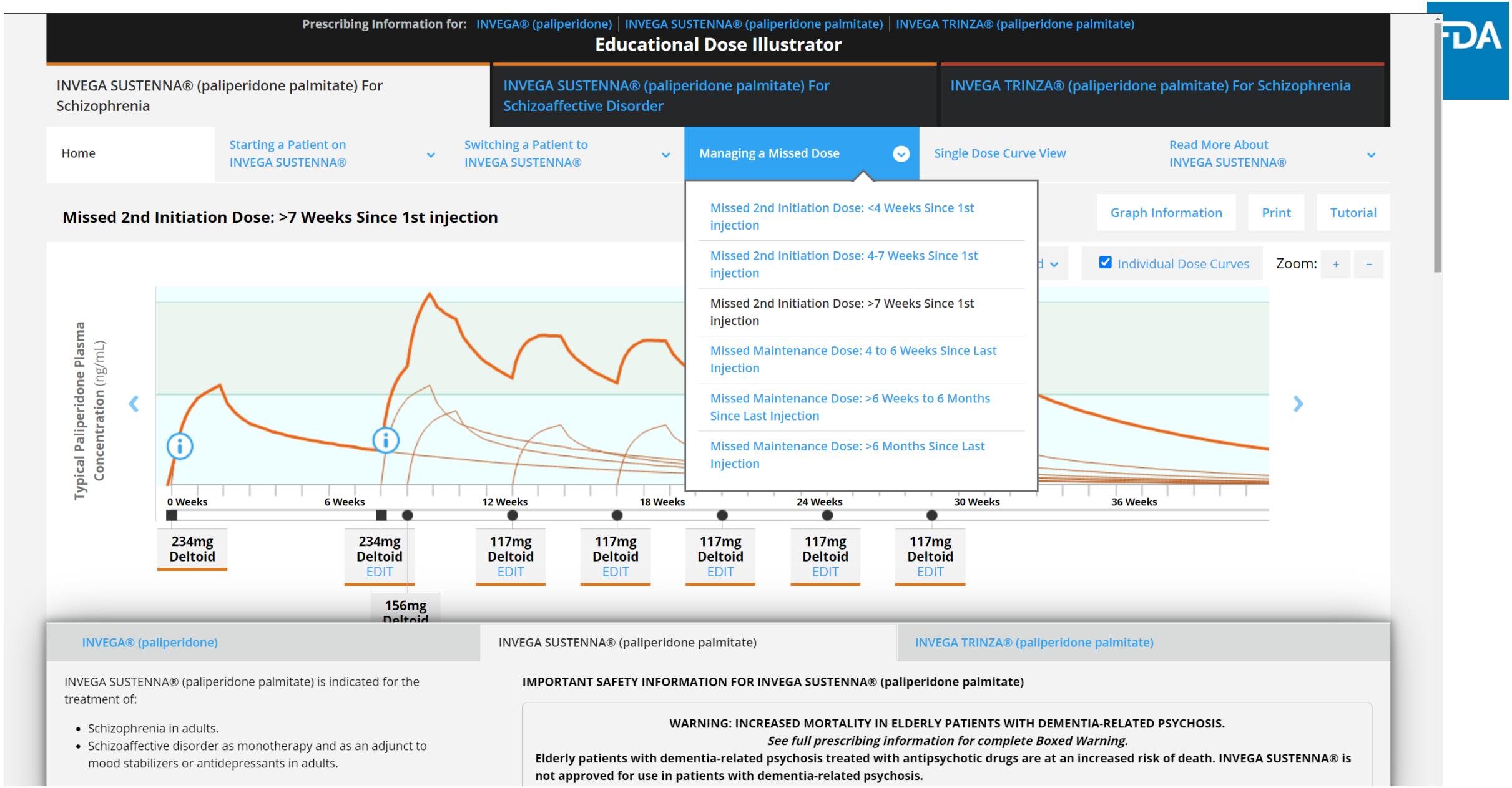
INVEGA SUSTENNA® (paliperidone palmitate) is indicated for the treatment of:

- Schizophrenia in adults.
- Schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants in adults.

IMPORTANT SAFETY INFORMATION FOR INVEGA SUSTENNA® (paliperidone palmitate)

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS.
See full prescribing information for complete Boxed Warning.
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



https://www.educationaldoseillustrator.com/pp1m/schizophrenia

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Case 2: Edoxaban

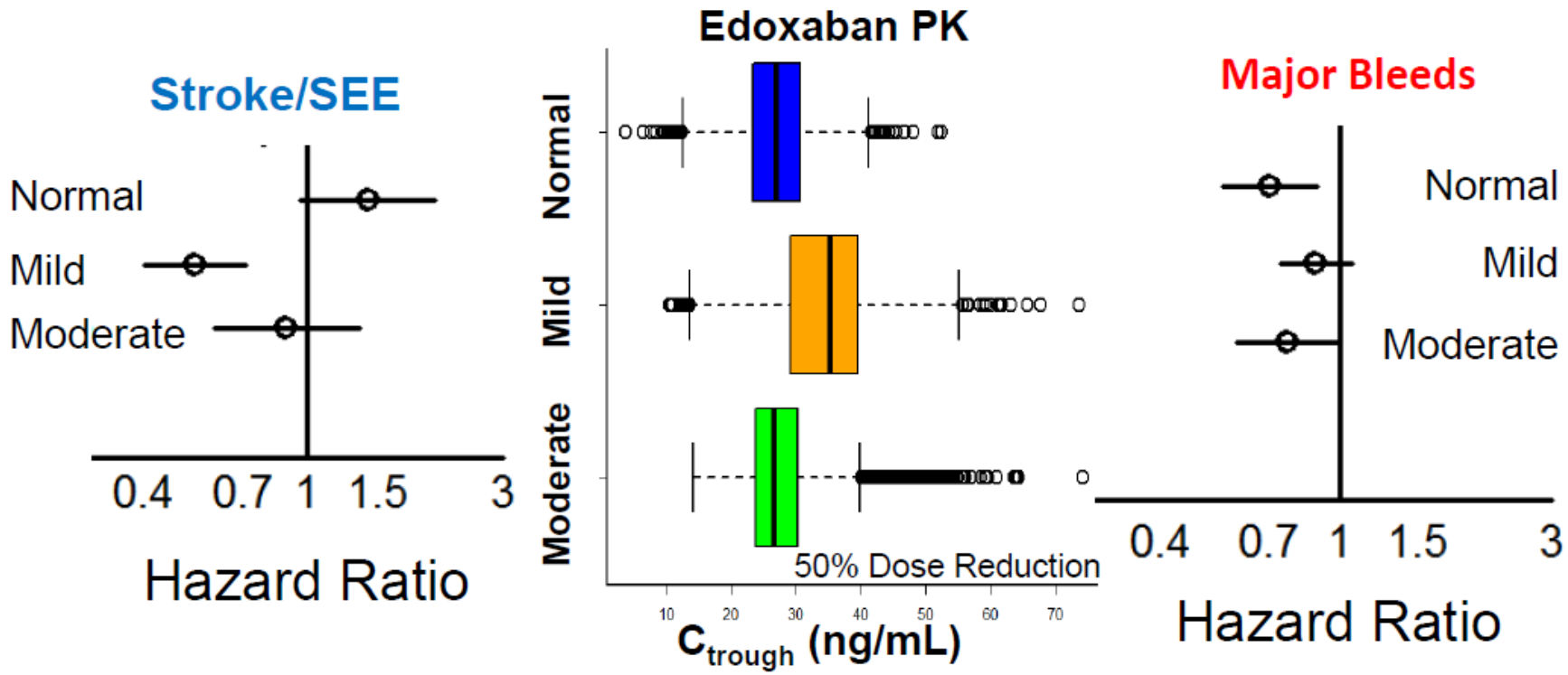
Dose Optimization for Subgroups

- **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

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

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



https://wayback.archive-it.org/7993/20170405211258/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM421612.pdf

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Dose Optimization PMC/PMR

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

Dose Optimization PMC/PMR

Year approved	Drug name (brand name)	Indications	Approved highest maintenance dose in adults[a]	Comments[b]
2011	Gabapentin enacarbil (Horizart)	Restless legs syndrome (RLS)	600 mg	PMR: 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
2011	Vilazodone (Viibryd)	Major depressive disorder (MDD)	40 mg	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
2010	Dalfampridine (Ampyra)	Multiple sclerosis (MS)	10 mg twice daily	PMC: to evaluate the efficacy of 5-mg twice-daily dose in MS
2010	Cabazitaxel (Jevtana)	Hormone-refractory metastatic prostate cancer (mHRPC)	25 mg/m^2 every 3 weeks	PMR: to compare a lower dose (20 mg/ m^2) with 25 mg/m^2 in mHRPC
2010	Fingolimod (Gilenya)	Multiple sclerosis	0.5 mg daily	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
2010	Lurasidone (Latuda)	Schizophrenia	160 mg	PMC: to identify the lowest effective dose; to evaluate with a dose lower than 40 mg (e.g., 20 mg daily)
2009	Asenapine (Saphris)	Schizophrenia and bipolar mania	10 mg twice daily	PMC: to identify the lowest effective dose; to study a dose <10 mg twice daily (e.g., 5 mg twice daily) in bipolar mania and to study a dose <5 mg twice daily (e.g., 2.5 mg twice daily) in schizophrenia
2008	Rilonacept (Arcalyst)	Cryopyrin-associated periodic syndrome	160 mg weekly	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
2008	Desvenlafaxine (Pristiq)	MDD	50 mg	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
2006	Paliperidone (Invega)	Schizophrenia	12 mg	PMC: to conduct a study to explore for a minimal effective dose

Is This the Dose for You?: The Role of Modeling, S-M Huang, A Bhattaram, N Mehrotra and Y Wang, *Clinical Pharmacology & Therapeutics* (2013); 93 2, 159–162

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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 Wang[1], Y Harigaya[2], M Cavaillé-Coll[3], P Colangelo[2] and KS Reynolds[2]

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

T Dumortier[1], M Looby[1], O Luttringer[1], G Heimann[2], J Klupp[3], G Junge[3], S Witte[1], R VanValen[4] and D Stanski[5]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 97 NUMBER 4 | APRIL 2015

Story Translated to Chinese by NMPA

CDE文章||定量药理学在确定非劣效试验界值中的作用

2018-02-24 16:00 设计 / 药物

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

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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**

Two Advisory Meetings

News > Medscape Medical News

Advisory Panel Unanimously in Favor of Boceprevir for HCV

Emma Hitt, PhD
April 29, 2011

0 Read Comments

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.

News > Medscape Medical News

Telaprevir for HCV Receives Advisory Panel's Vote of Approval

Emma Hitt, PhD
April 29, 2011

0 Read Comments

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.

https://www.medscape.com/viewarticle/741821

Publications and Praise from Experts

HEPATOLOGY AASLD

Viral Hepatitis | Free Access

Response-guided telaprevir therapy in prior relapsers? The role of bridging data from treatment-naïve and experienced subjects†‡§

Jiang Liu, Pravin R. Jadhav, Shashi Amur, Russell Fleischer, Thomas Hammerstrom, Linda Lewis, Lisa Naeger, Jule 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 | Citations: 13

HEPATOLOGY AASLD

Viral Hepatitis | Free Access

Boceprevir dosing for late responders and null responders: The role of bridging data between treatment-naïve and -experienced subjects†‡§¶

Jeffry Florian, 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

First published: 18 May 2012 | https://doi.org/10.1002/hep.25843 | Citations: 11

HEPATOLOGY AASLD

Editorial | Free Access

The FDA, bridging data, and hepatitis C†‡

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

First published: 29 November 2012 | 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.[6,7] These analyses have far - ranging implications for patients, clinicians, and for clinical investigators."

Many More Examples

Drug	Indication
Clevidipine	Acute hypertension
Paricalcitrol	Hyperthyroidism associated with chronic renal failure
Paliperidone ER	Adolescent Schizophrenia
Mirabegron	over-reactive bladder
Pralidoxime	Chemical poisonings for peds
Zosyn	Intra-abdominal infections
Trileptal	seizure
Topomax	seizure
Busulfan	chronic myelogenous leukemia
Canakinumab	Cryopyrin-Associated Periodic Syndromes
Raxibacumab	Inhalational Anthrax
Boceprevir	HCV
Telaprevir	HCV
Danuravir	HIV
Epinephrine	severe allergic reactions
Nexium IV	GERD patients with a history of erosive esophagitis
Levocetrizine	allergic rhinitis
Danuravir	HIV
Sofosbuvir	HCV
Dapagliflozin	Diabetes
…	…

Dose Adjustment Based on Models

Drug	Specific question(s) addressed using PBPK	Links to reviews and labels
Sildenafil injection	Effect of a strong CYP3A inhibitor on intravenous sildenafil exposure (vs. oral sildenafil)	Review: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022473s000_ClinPharmR.pdf Label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022473s003lbl.pdf
Diltiazem	Interaction of diltiazem with simvastatin	Review: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021392s014lbl.pdf Label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019766s087s088lbl.pdf; see also the label for simvastatin
Ponatinib	Effect of a strong CYP3A inducer (rifampin) on ponatinib exposure	Review: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203469Orig1s000ClinPharmR.pdf Label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203469lbl.pdf
Rivaroxaban	Assessing a complex and multiple interaction scenario: subjects with renal impairment and coadministered a combined P-gp and CYP3A4 inhibitor (weak or moderate)	Review: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022406Orig1s000ClinPharmR.pdf Label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022406s007lbl.pdf
Macitentan	Effect of a strong CYP3A inhibitor on macitentan steady-state exposure	Review: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204410Orig1s000ClinPharmR.pdf Label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204410s000lbl.pdfRefs. 19, 20
Ibrutinib	Effect of a moderate CYP3A inducer or inhibitor on ibrutinib exposure	Review: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf Label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205552s000lbl.pdf
Simeprevir	Assessing the significance of a transporter (OATP1B1/3) on simeprevir disposition	Review: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205123Orig1s000ClinPharmR.pdf Label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205123s001lbl.pdf

Physiologically based pharmacokinetic modeling: from regulatory science to regulatory policy, Sinha V, Zhao P, Huang SM, Zineh I, Clin Pharmacol Ther. 2014 May;95(5):478-80

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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 Warning Letter

FDA Drug Safety Communication: FDA warns about serious liver injury with Ocaliva (obeticholic acid) for rare chronic liver disease

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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-Antiarrhythmic 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

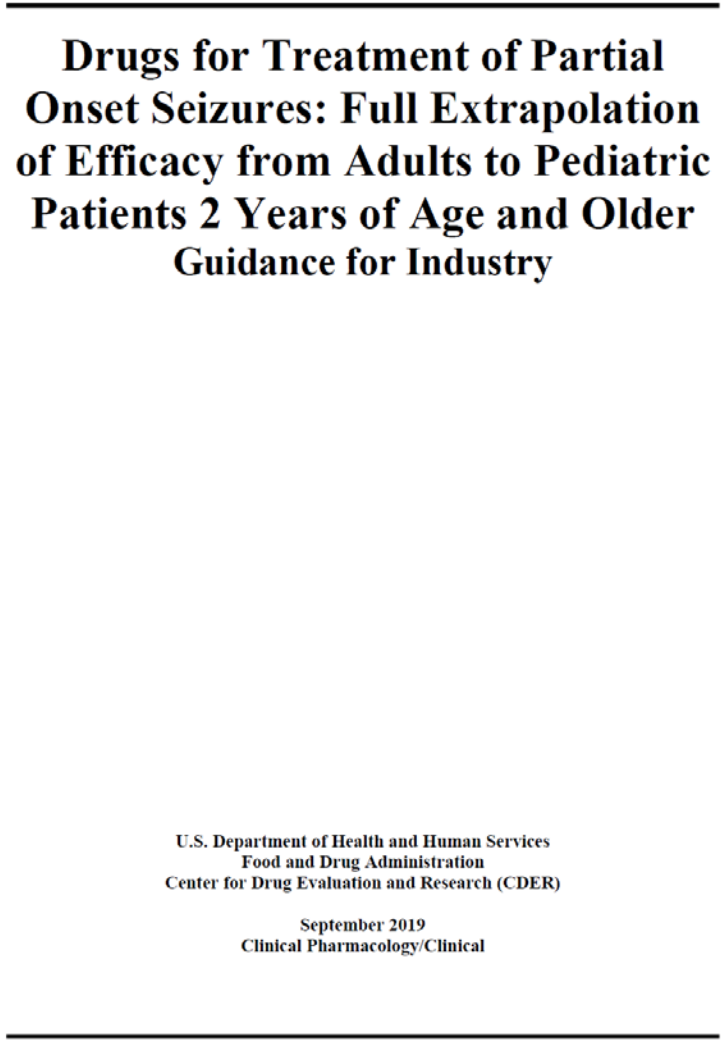
- **Collaboration among Pediatric Epilepsy Academic Consortium on Extrapolation (PEACE), University of Maryland and FDA**
- **Efforts to make pediatric drug development more efficient**
- **Full extrapolation already applied for monotherapy of partial onset seizures (POS)**
- **To support full extrapolation 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.**

- **<u>Required information</u> 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.**

New FDA Guidance


Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 2 Years of Age and Older
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

September 2019
Clinical Pharmacology/Clinical

"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 precision[4]. 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."

[4]Wang Yaning, Jadhav PR, Lala M, and Gobburu JV, 2012, Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies, J Clin Pharmacol, 52(10):1601–1606.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drugs-treatment-partial-onset-seizures-full-extrapolation-efficacy-adults-pediatric-patients-2-years

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)**

J Clin Pharmacol. 2020 Jul;60(7):848-859. doi: 10.1002/jcph.1580. Epub 2020 Jan 28.

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.**

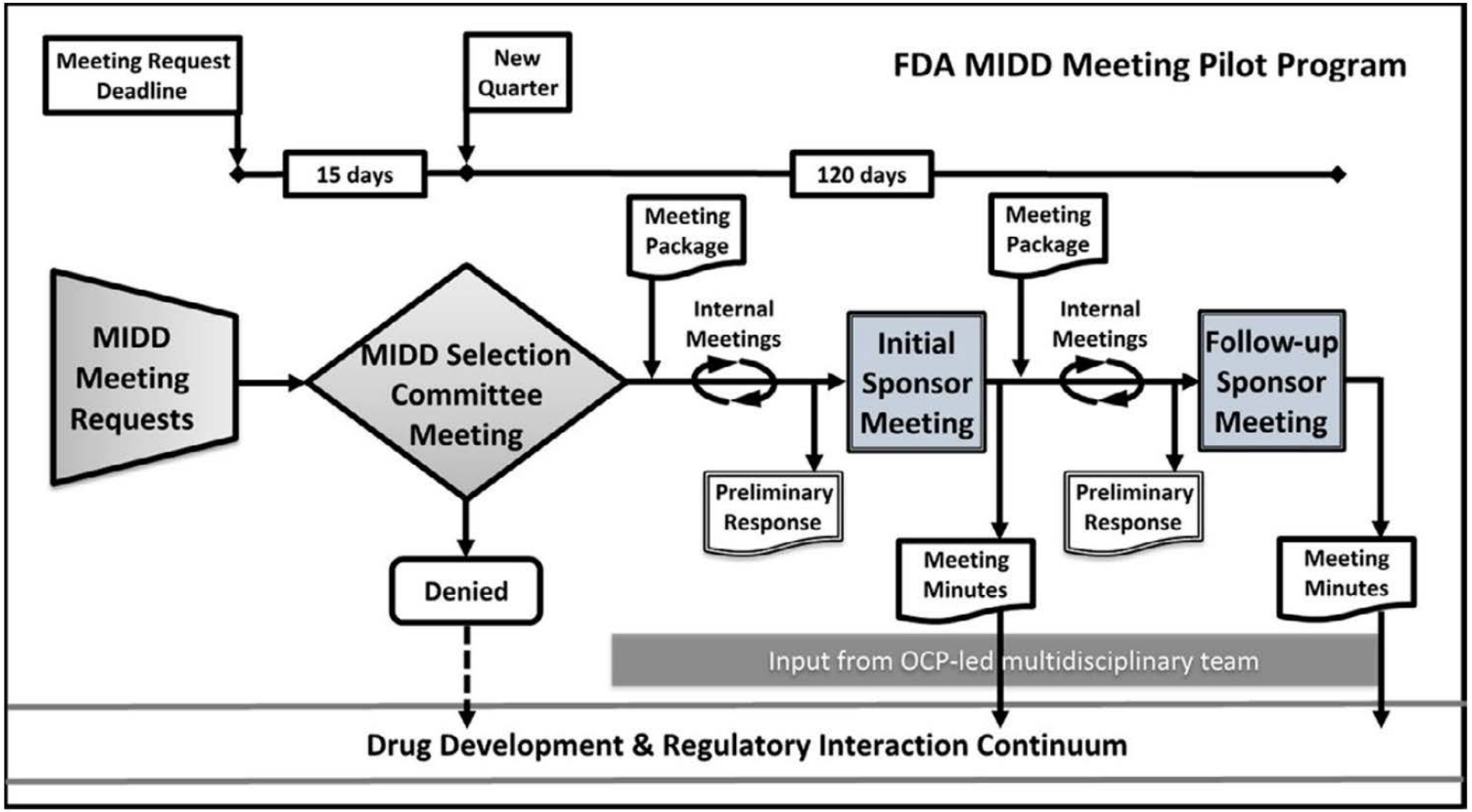
- **FDA will convene a series of workshops to identify best practices for MIDD.**
  - **Physiologically-based pharmacokinetic modeling**
  - **Design analysis and inferences from dose-exposure-response studies**
  - **Disease progression model development, including natural history and trial simulation**
  - **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.**

https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf

MIDD Pilot Meeting Process



Madabushi R et al., The US Food and Drug Administration's Model-Informed Drug Development Paired Meeting Pilot Program: Early Experience and Impact. Clin Pharmacol Ther. 2019 May 13

MIDD Submissions to FDA 1st PDUFA VI Year

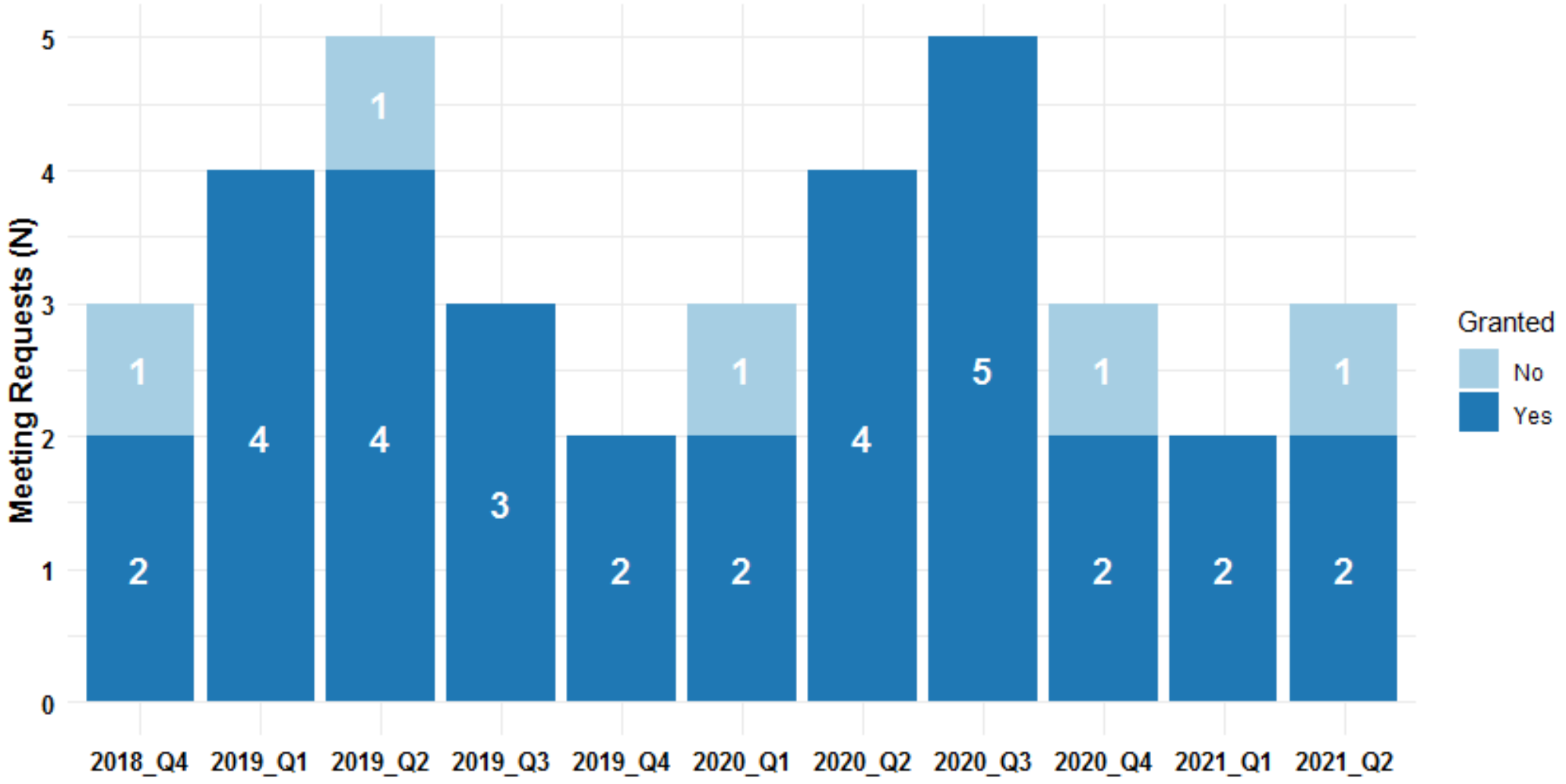
Table 1 The US Food and Drug Administration's model-informed drug development Paired Meeting Pilot Program: first-year submissions

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

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).

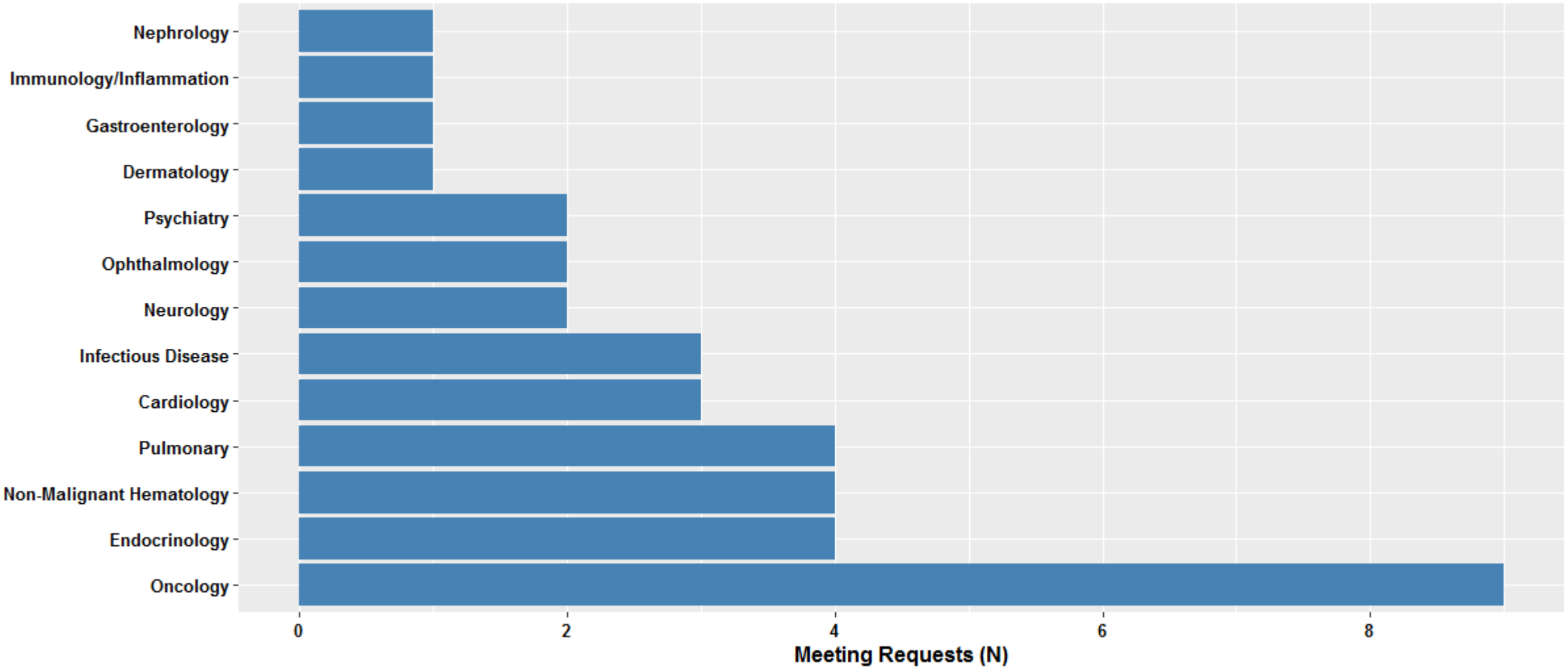
Madabushi R et al., The US Food and Drug Administration's Model-Informed Drug Development Paired Meeting Pilot Program: Early Experience and Impact. Clin Pharmacol Ther. 2019 May 13

Quarterly Meeting Requests



Total: 37

Therapeutic Areas



Total: 37

Drug Development Phase

Clinical Phase	Count
Preclinical/FIH, Phase I	4
Phase 1, Phase 2	1
Phase 2	7
Phase 2, Phase 3	9
Phase 3	6
Phase 3, Post-approval	3
Post-approval	7

MIDD Applications

MIDD Application	Count
Clinical trial simulation/clinical trial design	2
Clinical trial simulation/clinical trial design, Supportive evidence of efficacy	1
Dose selection/optimization	9
Dose selection/optimization, Clinical trial simulation/clinical trial design	20
Dose selection/optimization, Clinical trial simulation/clinical trial design, Supportive evidence of efficacy	1
Dose selection/optimization, Predictive or mechanistic safety	1
Dose selection/optimization, Predictive or mechanistic safety, Clinical trial simulation/clinical trial design	1
Dose selection/optimization, Supportive evidence of efficacy	1
Predictive or mechanistic safety, Dose selection/optimization, Clinical trial simulation/clinical trial design, Supportive evidence of efficacy	1

Quantitative Methods

Method	Count
Drug-disease-trial, Population Pharmacokinetic, Semi-mechanistic PK/PD	1
Drug-disease-trial, Semi-mechanistic PK/PD, Population Pharmacokinetic	1
Exposure-Response	3
Exposure-Response, Dose-response	1
Exposure-Response, Dose-response, Population Pharmacokinetic	1
Exposure-Response, Population Pharmacokinetic	12
Exposure-Response, Population Pharmacokinetic, Drug-disease-trial, Semi-mechanistic PK/PD	1
Exposure-Response, Semi-mechanistic PK/PD	1
Model-based-meta-analyses	1
Physiologically Based Pharmacokinetic	1
Population Pharmacokinetic	3
Quantitative Systems Pharmacology	2
Quantitative Systems Pharmacology, Drug-disease-trial	3
Semi-mechanistic PK/PD	5
Semi-mechanistic PK/PD, Drug-disease-trial	1

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

Calendar No. 152

114TH CONGRESS, 1st Session | SENATE | REPORT 114–82 | July 16, 2015

- **"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/p3pn29t4jjp/

2021 New Alternative Methodologies

Commissioner of Food and Drugs
Stephen M. Hahn, MD

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

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

STATE OF THE ART

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

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Future:

- **MIDD pilot**
- **Mechanistic models**
- **Machine-learning models**
- **Real-world data/real-world evidence**

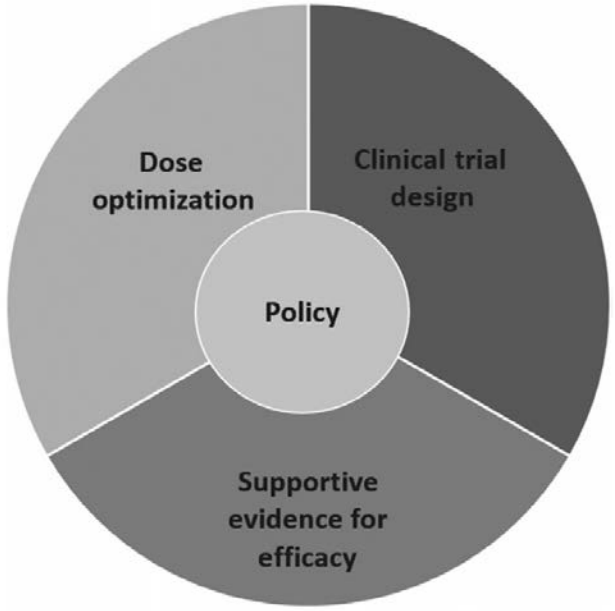

Figure 1 Regulatory application of model information drug development.

Table 3 Guidances endorsing model-informed drug development strategies in drug development and regulatory evaluation

Guidance name
Guidance for Industry: Population Pharmacokinetics
Guidance for Industry: Exposure-response Relationships-Study Design, Data Analysis, and Regulatory Applications
Physiologically Based Pharmacokinetic Analyses—Format and Content Guidance for Industry
Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 4 Years of Age and Older Guidance for Industry
ICH E4 Dose-Response Information to Support Drug Registration
Guidance for Industry: End-of-Phase 2A Meetings
Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of *In Vitro/In Vivo* Correlations
ICH E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs—Questions and Answers (R3)
Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment
Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases
Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment
Human Immunodeficiency Virus-1 Infection: Developing Systemic Drug Products for Pre-Exposure Prophylaxis
Respiratory Syncytial Virus Infection: Developing Antiviral Drugs for Prophylaxis and Treatment
Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment
Pulmonary Tuberculosis: Developing Drugs for Treatment
Pediatric Rare Diseases—A Collaborative Approach for Drug Development Using Gaucher Disease as a Model
General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products
Product Development Under the Animal Rule
Slowly Progressive, Low-Prevalence Rare Diseases with Substrate Deposition That Results from Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies
In Vitro Metabolism and Transporter Mediated Drug-Drug Interaction Studies
Clinical Drug Interaction Studies—Study Design, Data Analysis, and Clinical Implications
Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product
Hypertension: Developing Fixed Dose Combination Drugs for Treatment
Ulcerative Colitis: Clinical Trial Endpoints
Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling
E17 General Principles for Planning and Design of Multiregional Clinical Trials

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