U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

The Impact of MIDD during Phase 2 of New Drug Development - A Regulatory Perspective

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Disclaimer: This presentation reflects the views of the presenter and should not be construed to represent those of the FDA or the United States Government.

GUIDANCE DOCUMENT

End-of-Phase 2A Meetings

SEPTEMBER 2009

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Docket Number: FDA-2008-D-0514
Issued by: Center for Drug Evaluation and Research

This guidance provides information on end-of-phase 2A (EOP2A) meetings for sponsors of investigational new drug applications (INDs). The purpose of an EOP2A meeting is to facilitate interaction between FDA and sponsors who seek guidance related to clinical trial design employing clinical trial simulation and quantitative modeling of prior knowledge (e.g., drug, placebo group responses, disease), designing trials for better dose response estimation and dose selection, and other related issues. This guidance is intended to further FDA initiatives directed at identifying opportunities to facilitate the development of innovative medical products and improve the quality of drug applications through early meetings with sponsors.

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Leveraging Prior Quantitative Knowledge to Guide Drug Development Decisions and Regulatory Science Recommendations: Impact of FDA Pharmacometrics During 2004-2006

Yaning Wang, A. Venkatesh Bhattaram, Pravin R. Jadhav, Lawrence J. Lesko, Rajanikanth Madabushi, J. Robert Powell, Wei Qiu, He Sun, Dong S. Yim, Jenny J. Zheng, and Jogarao V. S. Gobburu

The End-of-Phase 2A meetings are proposed to identify opportunities to make innovative medical products available sooner and to increase the quality of drug applications through early meetings between sponsors and the FDA. This article summarizes the overall experience across 11 pilot End-of-Phase 2A meetings since 2004. Four case studies are presented in more detail to demonstrate the various issues and methods encountered at these meetings. Overall, industry and FDA scientists ranked these meetings to be "very helpful" (average score of 4 on a scale of 1 to 5). In almost all the instances the sponsors changed their drug development plans subsequent to these extensive quantitative analyses–based meetings. A draft Guidance is being developed to be issued in 2008, and we hope this initiative will be resourced by then.

Keywords: *Regulatory decisions; EOP2A meeting; modeling; simulation; FDA; drug development; pharmacokinetics; pharmacodynamics; pharmacometrics*

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EOP2A Cases

Table I Summary of all Meetings Between the FDA and Various Sponsors That Involved Extensive Quantitative Work to Guide Future Drug Development During 2004-2006

Meeting	Disease Area	Key Questions
1	Epilepsy	Registration trial dose selection
2	Anti-infective	Registration trial dose selection
3	HIV disease	Phase 2b and registration trial dose selection
4	Palliative treatment of advanced prostate cancer	Registration trial dose selection
5	Type 2 diabetes mellitus	Registration trial dose selection and design
6	Centrally active analgesic agent, acute and chronic pain	Registration trial dose selection and design
7	Long-term weight-loss agent	Registration trial dose selection and design
8	Anticoagulation, deep vein thrombosis (DVT)	Phase 2b dose selection
9	Vasomotor symptoms	Phase 2b dose selection
10	Sleep disorder	Registration trial dose selection and design
11	Life-threatening infection	Registration trial dose selection and design

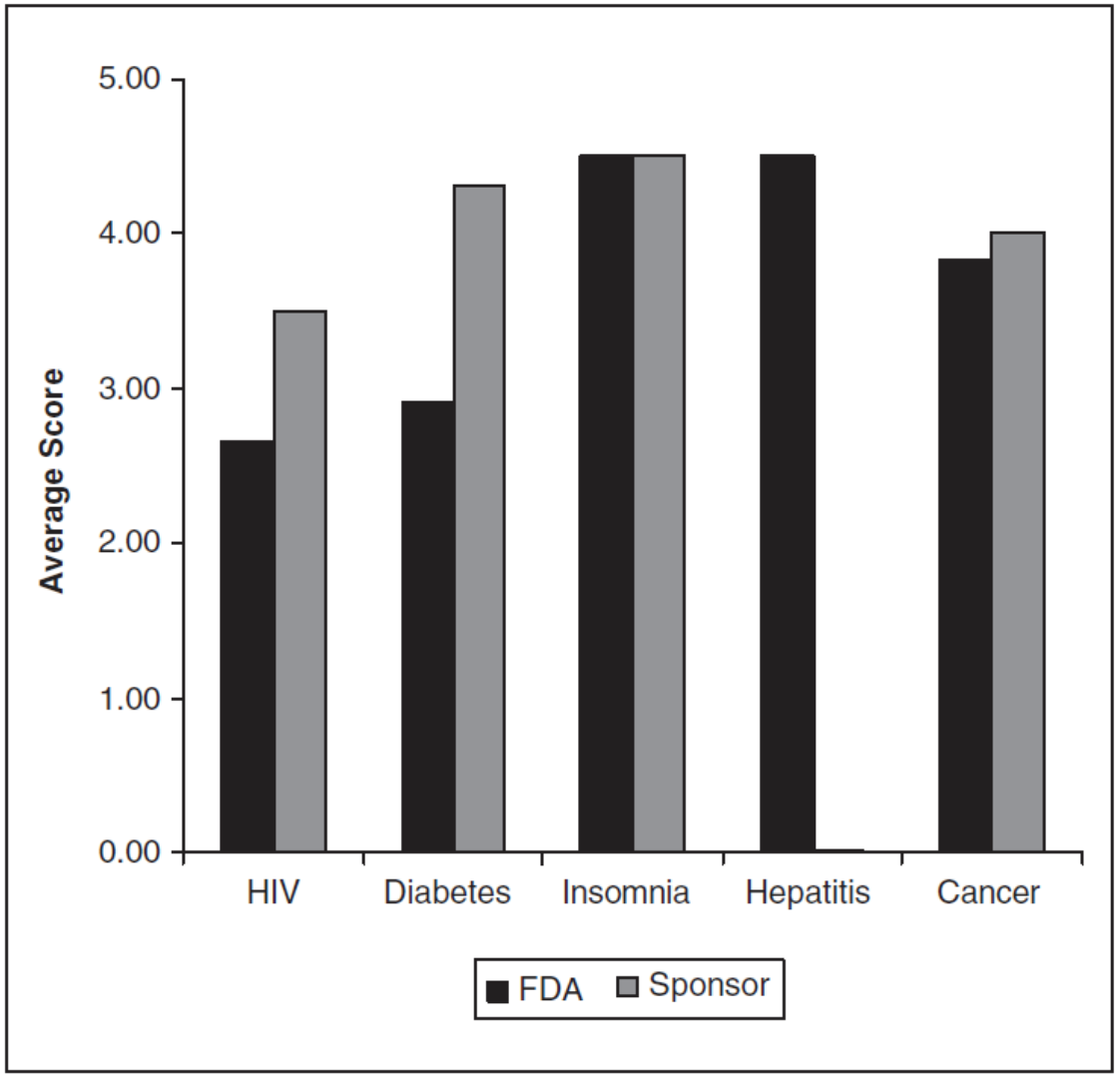

Figure 1. Average score on a 1 (no value) to 5 (pivotal) scale for the overall value of the EOP2A meeting to discuss dose and trial design selections based on quantitative analyses.

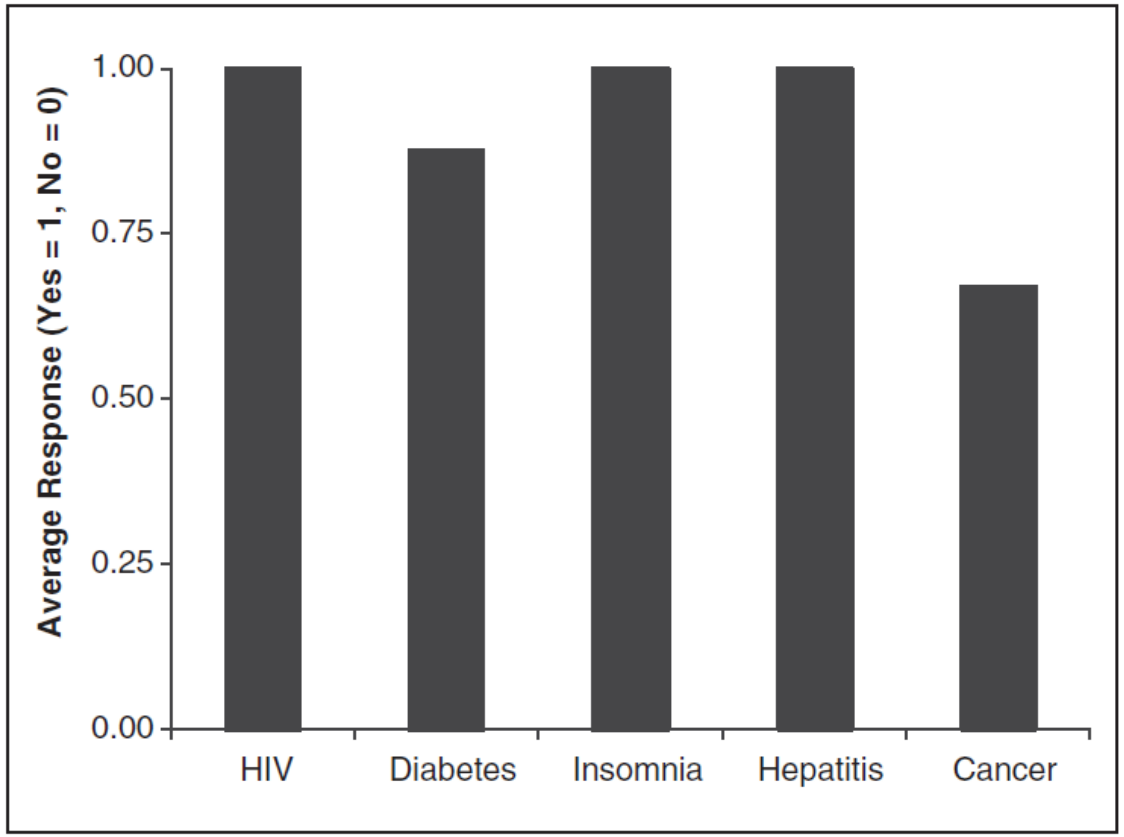

Figure 2. Average response from the sponsors to the question "Did the interaction with the FDA lead to a change in the drug development plan?" The score was averaged across "yes" (treated as 1) and "no" (treated as 0) answers. For example, an average response of 1 indicates all and 0.5 indicates 50% of the sponsor representatives concluded that the meeting changed the development plan.

FDA Comments (paraphrased where necessary to blind identity of compounds and disciplines)
"The reviewers don't have the time to do the sponsor's work for them. Doesn't make sense to work this way in light of the vast differences in resources between us and industry."
"Although most people considered the meetings 'very helpful,' I thought it added more than that. This is because of the previous drug's experience. I strongly believe that we were able to apply our lessons learned from previous drugs to this new drug development strategy."
"Sponsor's analysis was sufficient to conclude that dose selection was appropriate. Modeling by FDA had minimal impact on overall conclusions, and there were concerns with assumptions made in the model."
"The suggestions for a change in development strategy will prevent the sponsor from conducting a large, long study that puts patients at undue risk. The suggestions will help design a better phase 3 study, if benefit/risk is acceptable."
"(As a result of the EOP2A modeling work) we expect fundamental dosing changes (eg, duration, doses)."
"This pharmacometric assessment must be very resource-intensive, but it appears to be one of the most useful tools that FDA has to enhance drug development."

Sponsor Comments (paraphrased where necessary to blind identity of compounds and disciplines)
"(Sponsor) believes that insight gained from the discussion on endpoints and study design issues will be very helpful in enabling us to define an efficient and successful path forward to registration of our compound."
"Meeting was very efficient and well conducted by the agency and sponsor. The atmosphere of the meeting was very conducive to an open dialogue and bilateral idea sharing. I would only encourage the continuation of this meeting, its timing within the development cycle, and its notable openness/informality, which fostered the information sharing."
"The development plan for our compound was changed significantly based on feedback provided by FDA at this meeting. One specific example of change is changing phase 2 study designs to assure availability of sufficient data to confirm before committing to selection of dose and dosage interval for use in phase 3 studies."
"The technical discussion about the modeling and simulation approach in the development of this drug was of high quality and, therefore, very valuable. It is good to experience that the FDA supports the use of (new) biometrical techniques in drug development."
"Although the results were consistent with our initial thoughts, however, many details in the proposed plan were affected, including the safety evaluation."

External Commentaries

They Are From the Government and They Really Are Here to Help You

Raymond L. Woosley, MD, PhD

Keywords: *FDA; modeling; simulation; clinical trial*

Journal of Clinical Pharmacology, 2008;48:142-143
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Communicating With the FDA: The "Third Rail" of a New Model for Drug Development

Donald R. Stanski, MD, and John J. Orloff, MD

Keywords: *Drug development; biomarkers; modeling and simulation; FDA; communication*

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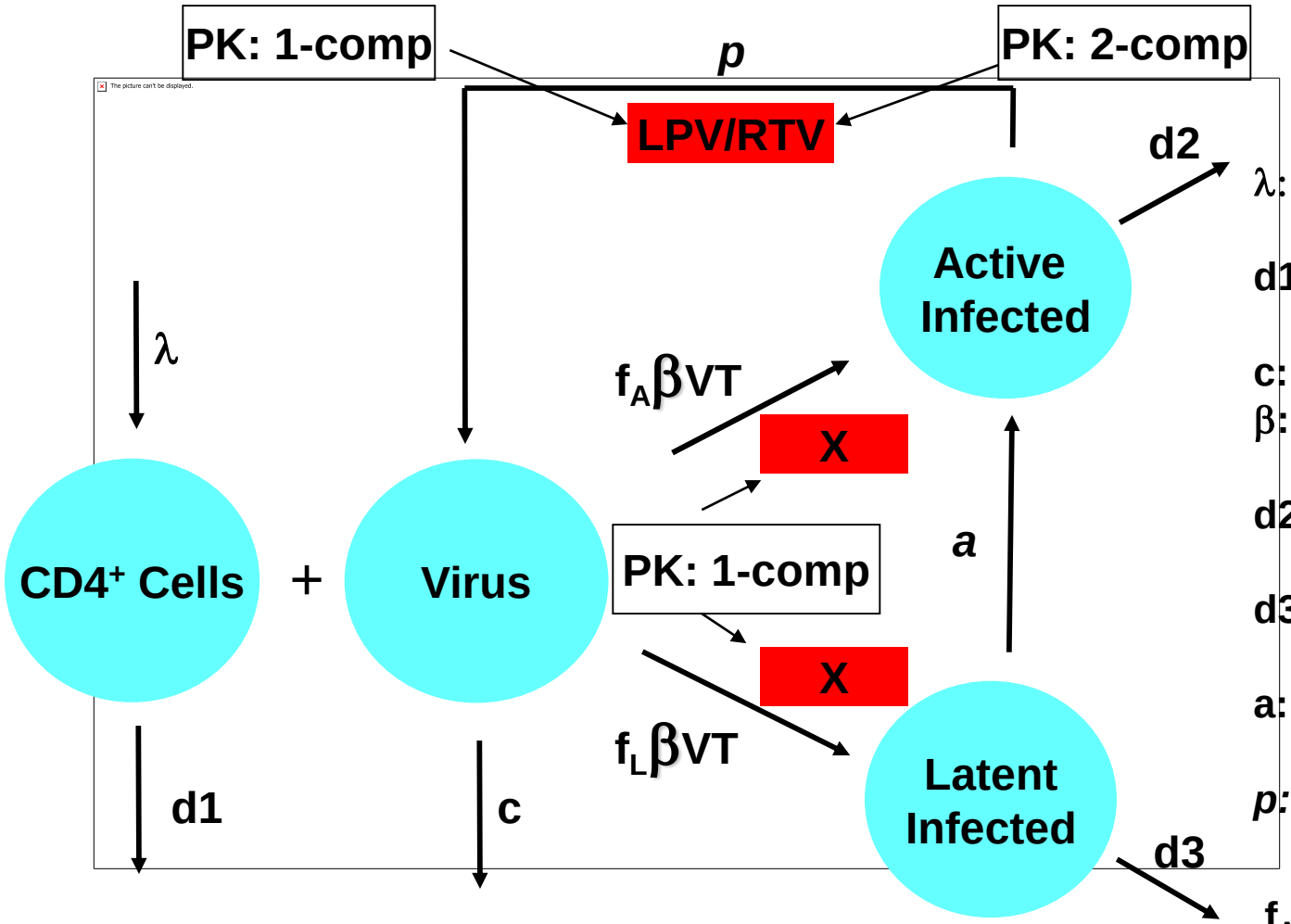
HIV Compound: Drug X

- Objective of an EOP2A meeting
  - Dose selection for phase 2B trial and the duration to select phase 3 dose
- Models involved
  - Disease model: viral dynamic model
  - Drug model
    - PK model for drug X
    - PK model for Kaletra (LPV/RTV)
    - PK interaction and PD interaction
  - Trial model
    - Compliance model
    - Drop out model

Viral Dynamic Model

Funk G. et al. *JAIDS* 26:397, 2001

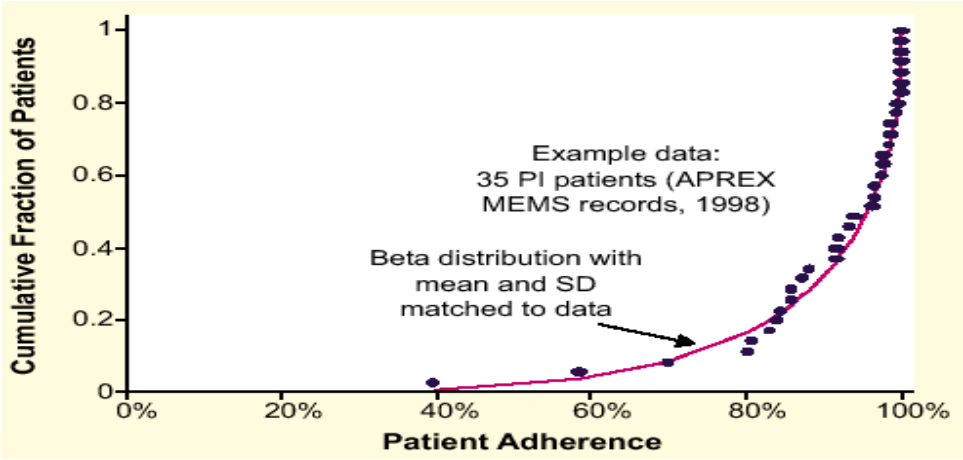


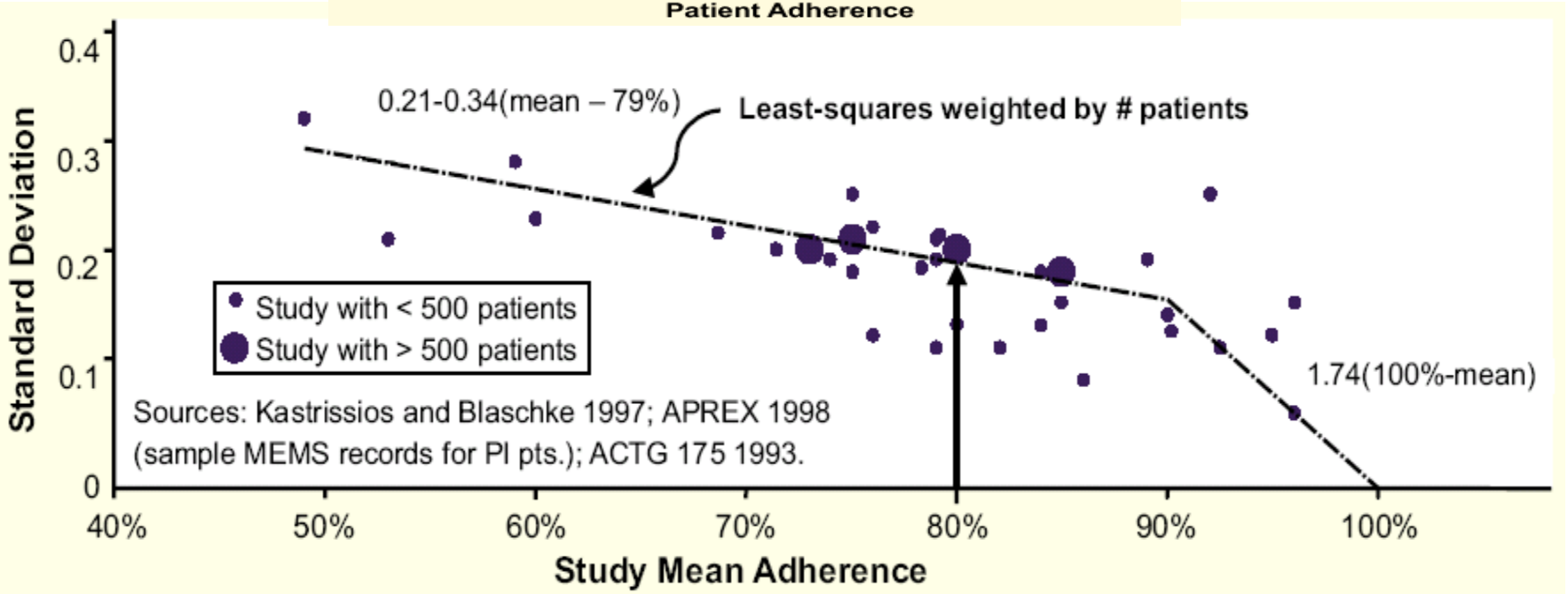
λ: production rate of target cell
d1: dying rate of target cell
c: dying rate of virus
β: infection rate constant
d2: dying rate of active cells
d3: dying rate of latent cells
a: reactivation rate of latent cells
p: *production* rate of virus

f_A=0.96 and f_L=0.03

Adherence Model

Beta (mean=0.8, SD=0.2)

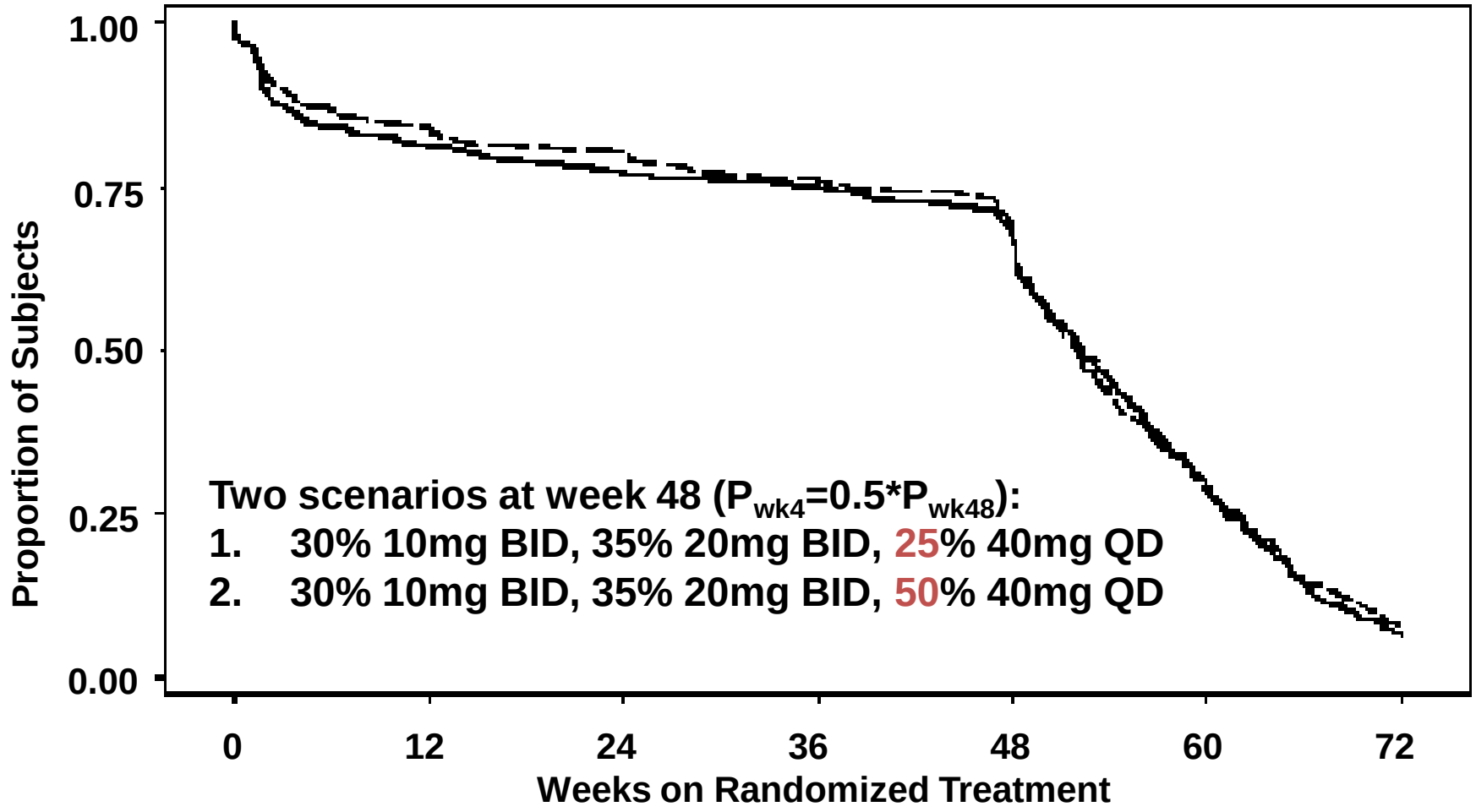




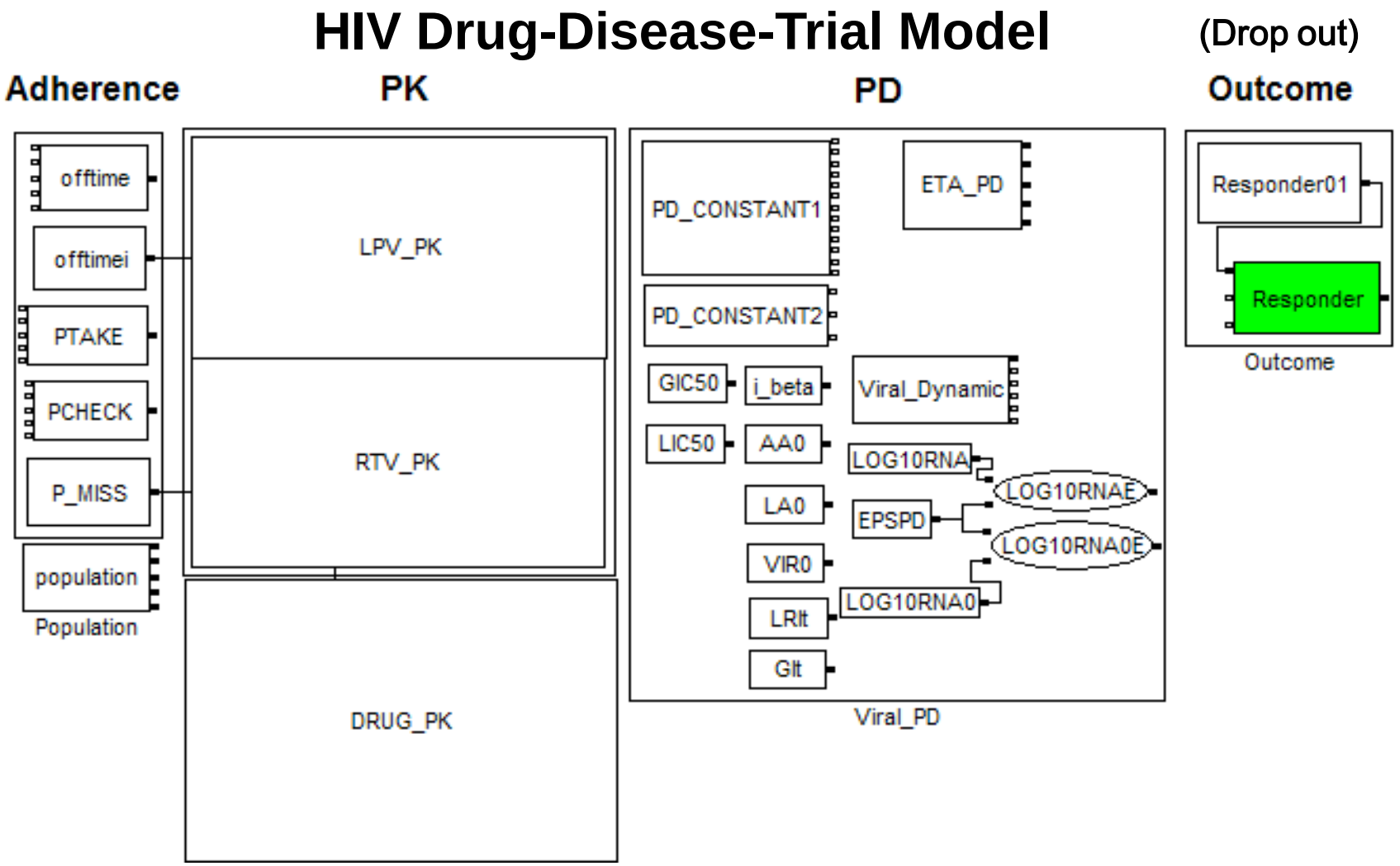
http://www.medadvocates.org/resources/conferences/4thPharmWkshp/indexkaletra.htm

Dropout Model

Biphasic Linear Model



Phase 2B Trial Simulation Based on Four Linked Models



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FDA Recommendations

- **BID regimen is preferable and a lower BID dose, instead of higher QD dose, is worth considering**
- **4 weeks is too short to select the dose based on efficacy. It is acceptable to use weeks 12-16 data for preliminary assessment (pick dose for Phase III trial) and week 24 for confirmation. Continue trial through week 48 for all doses.**
- **Kaletra (LPV/RTV) effect is so strong that it may be difficult to demonstrate Drug X dose-response in combination**
- **Dose selection may be driven by safety**

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.**

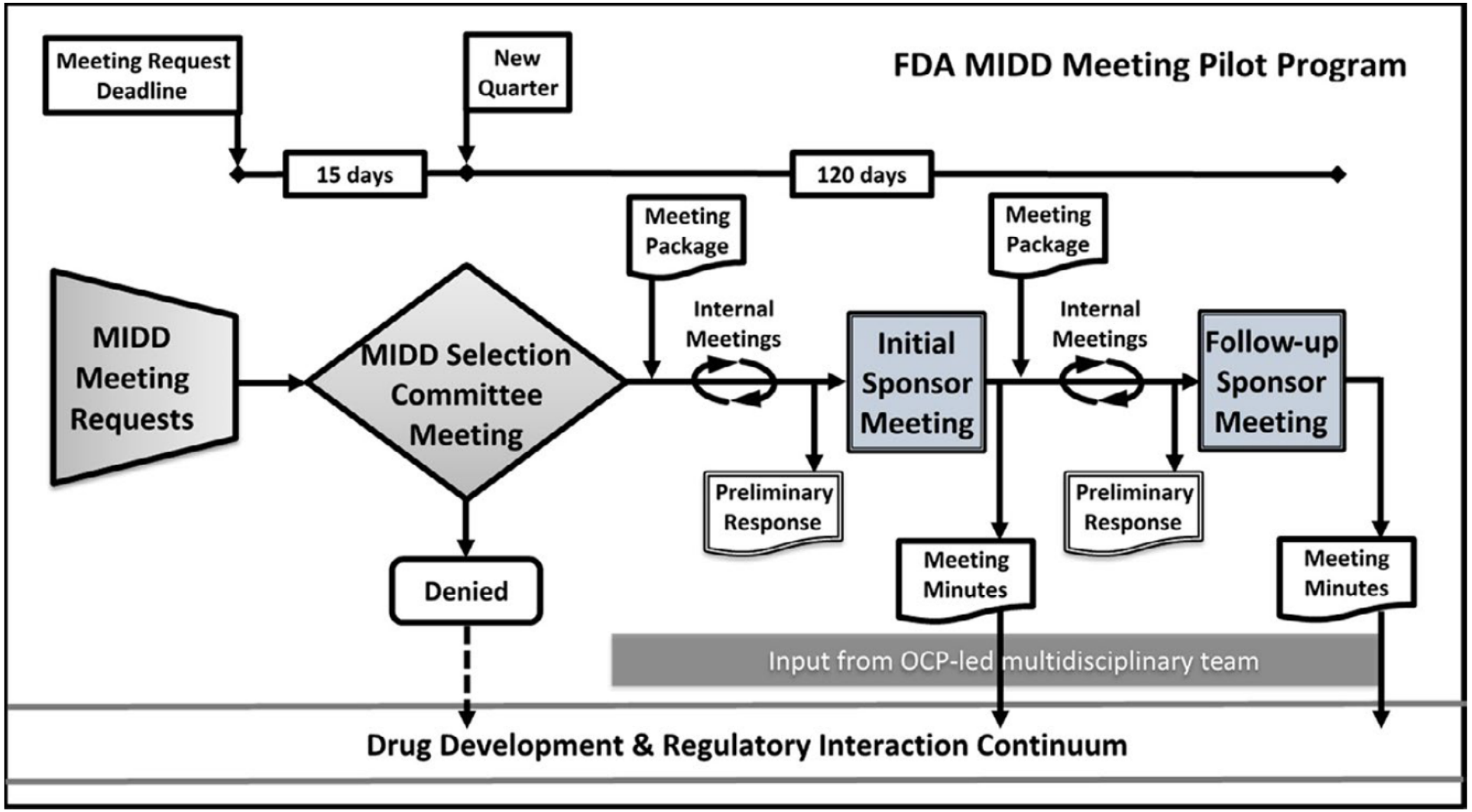
- **FDA will convene a series of workshops to identify best practices for MIDD.**
  - **Physiologically-based pharmacokinetic modeling**
  - **Design analysis and inferences from dose-exposure-response studies**
  - **Disease progression model development, including natural history and trial simulation**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

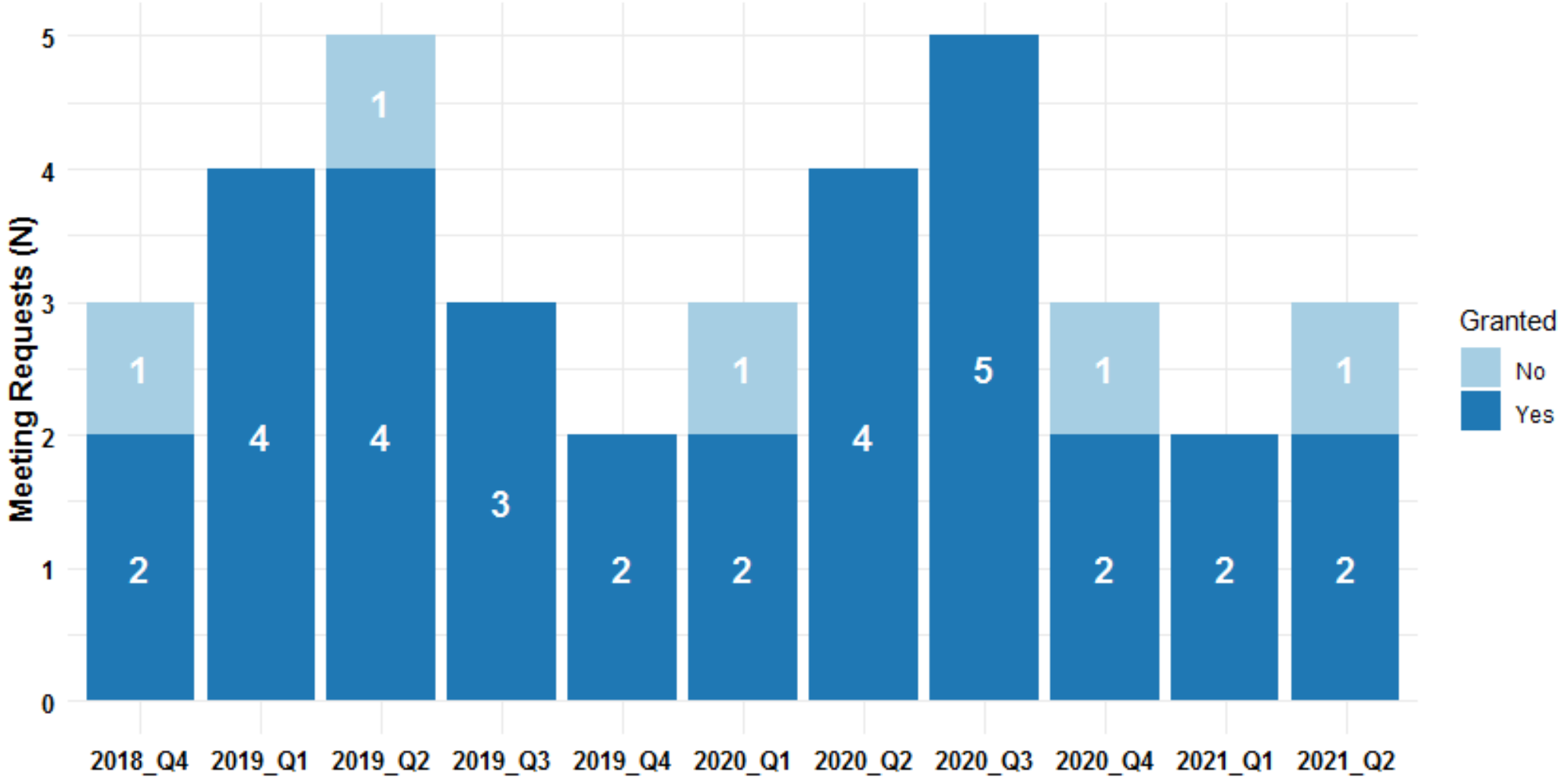
Table 1 The US Food and Drug Administration's model-informed drug development Paired Meeting Pilot Program: first-year submissions

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).

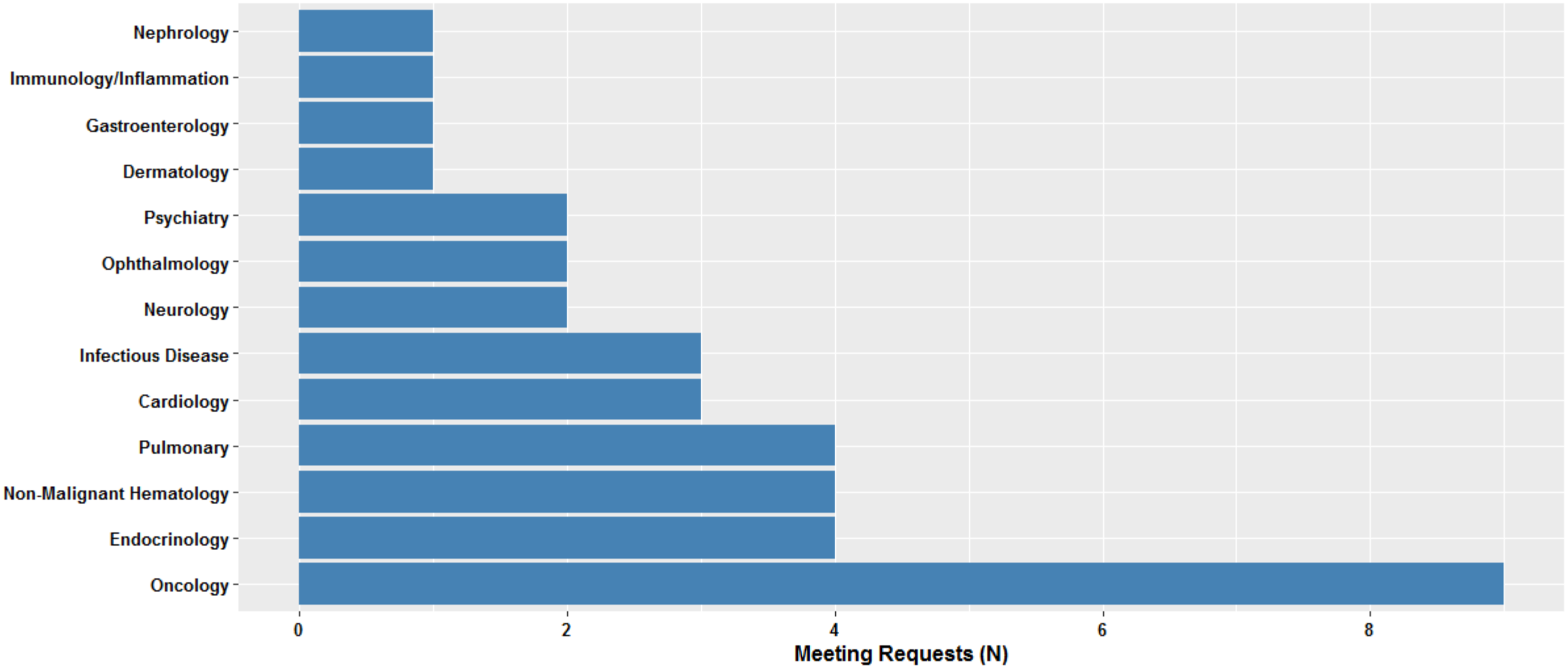
Madabushi R et al., The US Food and Drug Administration's Model-Informed Drug Development Paired Meeting Pilot Program: Early Experience and Impact. Clin Pharmacol Ther. 2019 May 13

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

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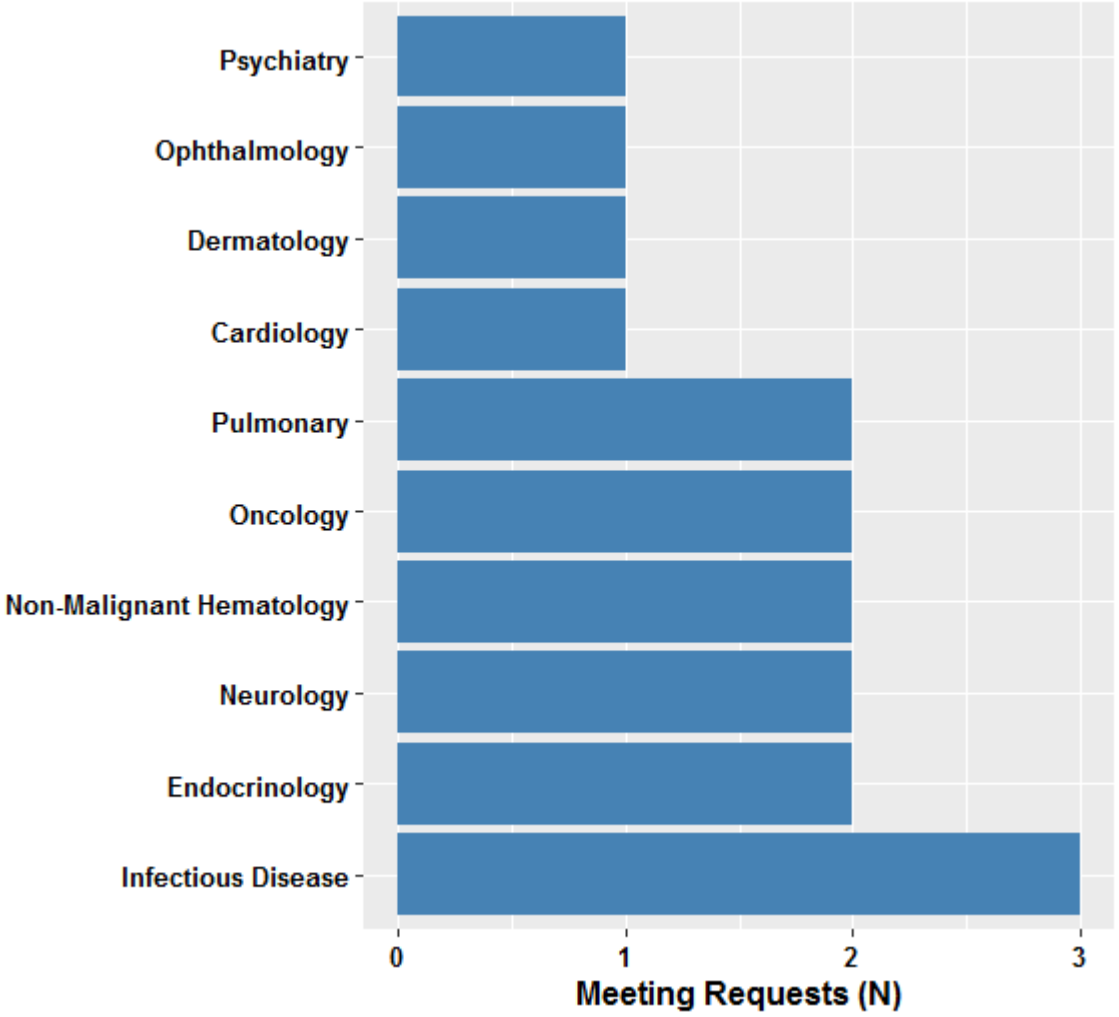
MIDD Applications

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

Phase 2 Specific Applications



MIDD Application	Count
Clinical trial simulation/clinical trial design, Supportive evidence of efficacy	1
Dose selection/optimization	4
Dose selection/optimization, Clinical trial simulation/clinical trial design	11
Dose selection/optimization, Predictive or mechanistic safety, Clinical trial simulation/clinical trial design	1

Method	Count
Drug-disease-trial, Population Pharmacokinetic, Semi-mechanistic PK/PD	1
Drug-disease-trial, Semi-mechanistic PK/PD, Population Pharmacokinetic	1
Exposure-Response, Dose-response	1
Exposure-Response, Dose-response, Population Pharmacokinetic	1
Exposure-Response, Population Pharmacokinetic	4
Exposure-Response, Semi-mechanistic PK/PD	1
Model-based-meta-analyses	1
Physiologically Based Pharmacokinetic	1
Population Pharmacokinetic	1
Quantitative Systems Pharmacology	1
Quantitative Systems Pharmacology, Drug-disease-trial	1
Semi-mechanistic PK/PD	3

Regulatory Impact

Impact	Count
Agreed on endpoints for use in trials , Aligned on MIDD approach/strategy, Alleviated the need for additional studies (i.e., fewer studies needed)	2
Aligned on MIDD approach/strategy	5
Aligned on MIDD approach/strategy, Aligned on trial dose selection and design	4
Smaller study needed (i.e., fewer treatment arms or fewer patients), Aligned on MIDD approach/strategy	2

Summary

- **Model-informed drug development (MIDD) has a long history of regulatory support.**

- **Models with different levels of complexities have been applied to help various decisions at different stages.**

- **MIDD activities under PDUFA VI provide additional momentum to apply quantitative methods in more areas of new drug development.**

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