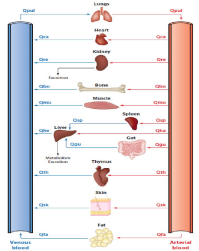
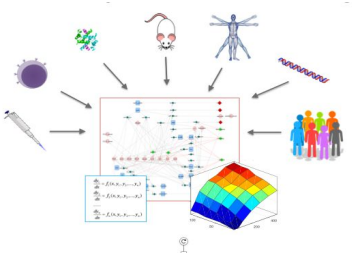
Advancing Clinical Pharmacology Innovation through Regulatory Policy

Michelle Rohrer, PhD
Senior Vice President
Global Head, Product Development Regulatory
Genentech, a Member of the Roche Group

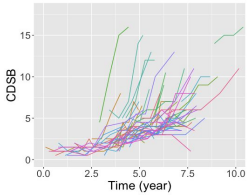
Model-Informed Drug Development Approaches



In-depth Kinetics:
PBPK

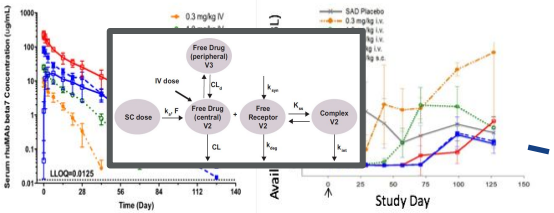


In-depth Dynamics:
QSP

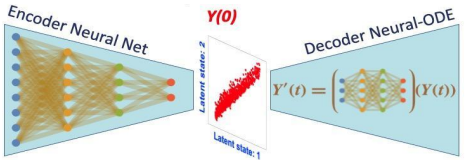


Disease Progression:
Disease Model

Emerging Data Source: *RWD*

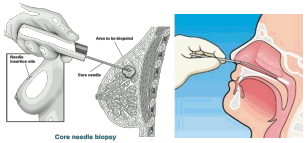


Drug Exposure and Response:
PK/PD & TMDD

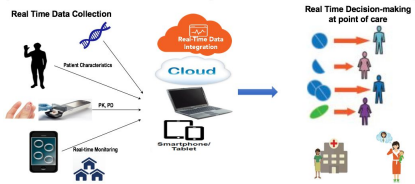


Emerging Approach: *AI/ML*

Model-Informed Drug Development



PK and PD at the site-of-action:
Tissue PK/PD, Receptor Occupancy

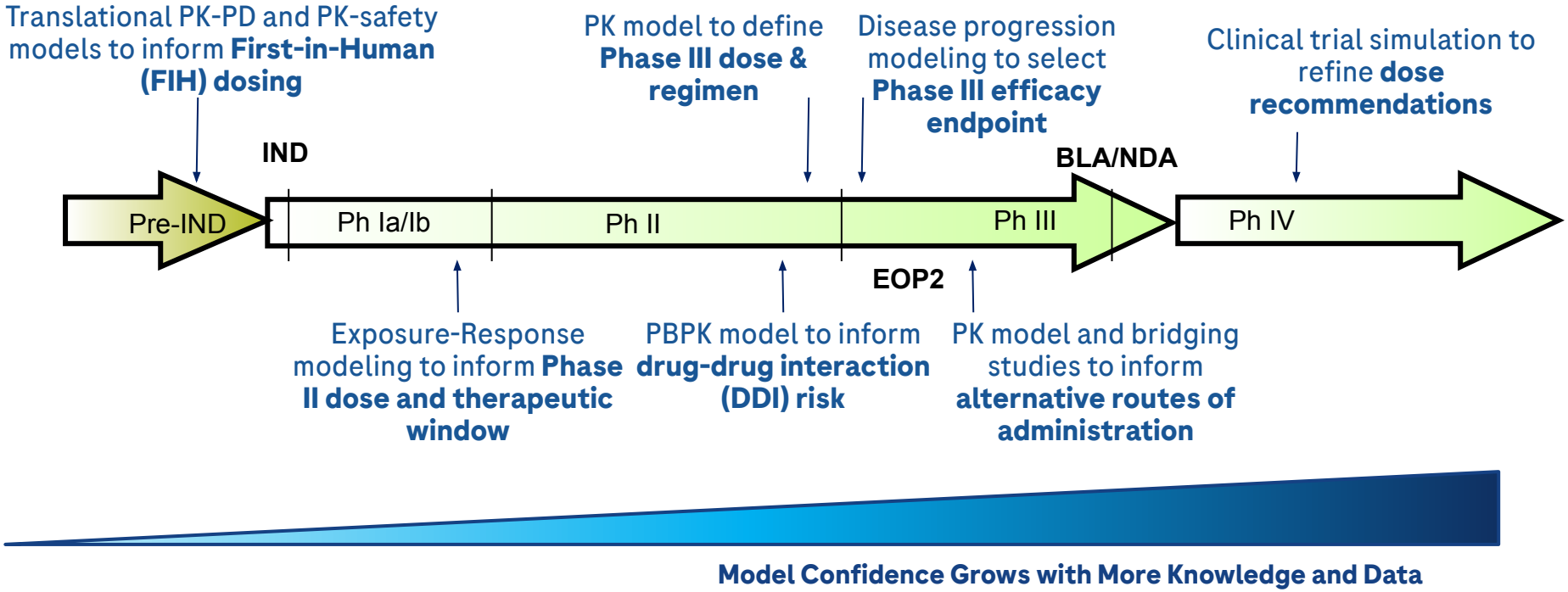


Emerging Application:
Algorithms for Personalized Dosing

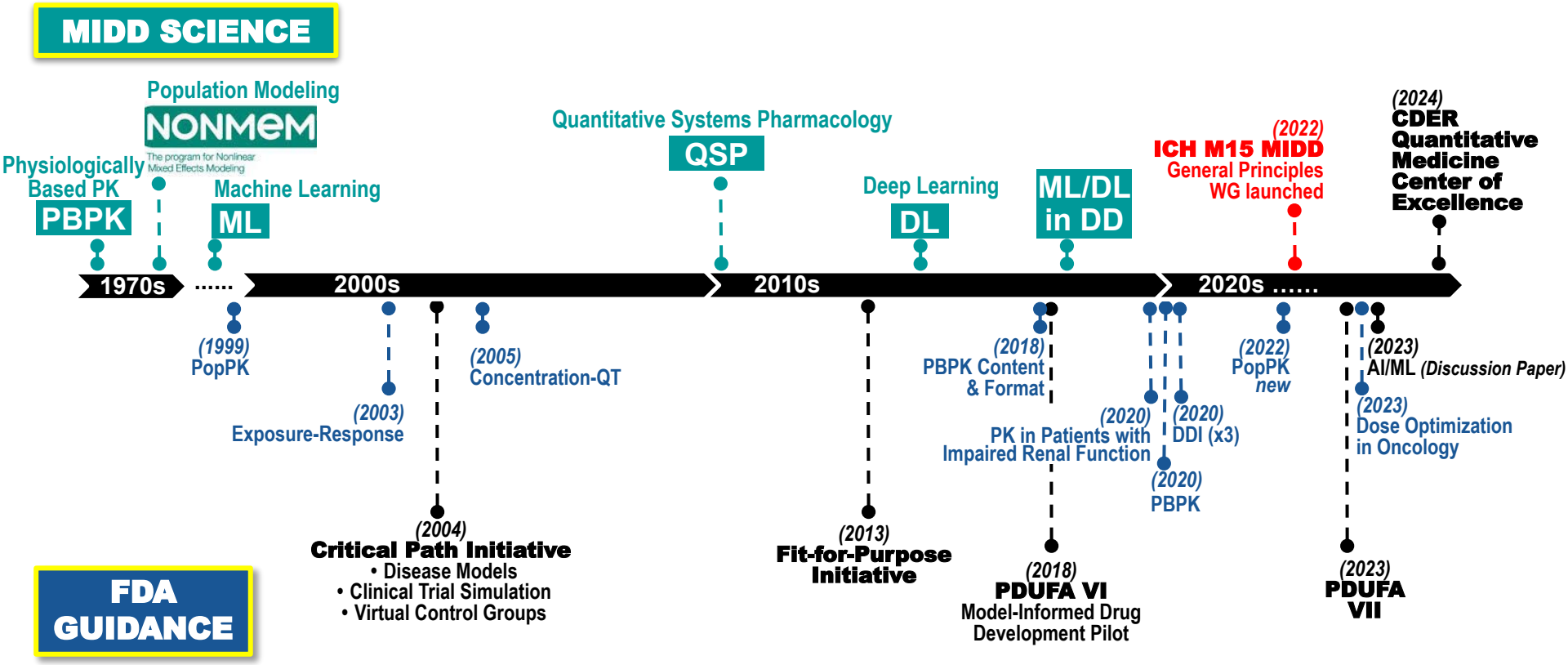
AI/ML – artificial intelligence/machine learning; PBPK – physiologically based pharmacokinetics; PK/PD – pharmacokinetics/pharmacodynamics; QSP – quantitative systems pharmacology; TMDD – target-mediated drug disposition

Application Across Drug Development Lifecycle

Select Examples



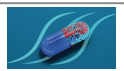
Progression of Science and Policy



AI/ML – artificial intelligence/machine learning; DL – deep learning; MIDD – model-informed drug development; NONMEM – nonlinear mixed effects modeling; PBPK – physiologically based pharmacokinetics; PDUFA – prescription drug user fee act; PopPK – population pharmacokinetics; QSP – quantitative systems pharmacology

Emerging Priorities: Project Optimus

Opportunities for Regulatory Action & Guidance to Advance Innovation



Project Optimus

Reforming the dose optimization and dose selection paradigm in oncology

ASCO

FDA/ASCO workshop

(2022&2023)

Getting the Dose Right: Optimizing Dose Selection Strategies in Oncology

AACR

2024 FDA/AACR workshop

Optimizing Dosages for Oncology Drug Products: quantitative approaches

Optimizing Dosing in Oncology Drug Development

Friends of Cancer Research Annual Meeting 2021

FRIENDS of CANCER RESEARCH

Describe current challenges to the implementation of dose-finding studies in oncology Discuss opportunities to improve dosing strategies given ongoing challenges Set expectations for dose-finding studies in the oncology pre-market setting Identify key considerations for selecting appropriate dose optimization strategies in oncology

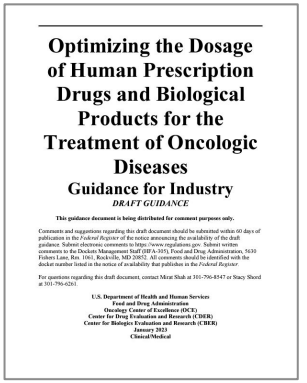
Dose Optimization during drug development: whether and when to optimize

Edward L. Korn ,PhD,, Jeffrey A. Moscow, MD,Boris Freidlin ,PhD, 2023

NIH NATIONAL CANCER INSTITUTE

We consider the relative merits of performing dose optimization earlier vs later in the drug development process and demonstrate that a considerable number of patients may be exposed to ineffective therapies unless dose optimization is delayed until after clinical activity or benefit of the new agent has been established. We conclude that patient and public health interests may be better served by conducting dose optimization after (or during) phase III evaluation, with some exceptions when dose optimization should be performed after activity shown in phase II evaluation.

FDA



Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Mirat Shah at 301-796-8547 or Stacy Shord at 301-796-6261.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
January 2023
Clinical/Medical

PAIN POINTS

"Guidance too generic, lack of clear tangible solutions"

"Always defer to 'case-by-case' is not helpful"

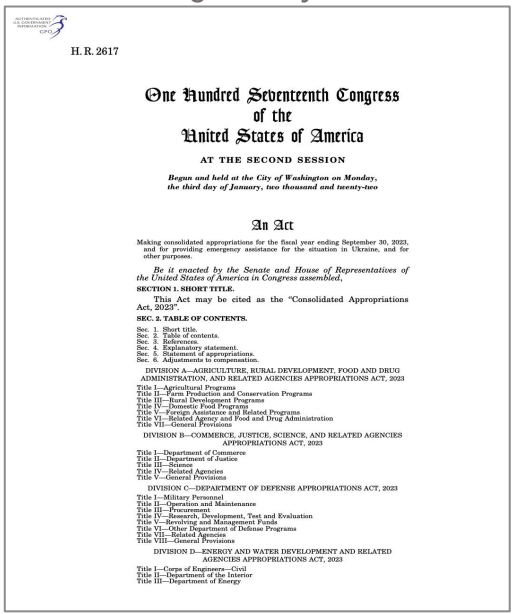
"Lack of regulatory consistency between divisions (heme vs solid tumor) and functions (OCE vs OCP)"

OPPORTUNITIES

- **General guiding principles that allow for flexibility while providing specific examples of fit-for-purpose use of different approaches**
- **Early regulatory communication to co-develop dose strategy**
- **Enhanced communication and alignment among divisions in FDA, and timely shared learning with industry**

Emerging Priorities: Diversity and Inclusion

Opportunities for Regulatory Action & Guidance to Advance Innovation



H. R. 2617

One Hundred Seventeenth Congress
of the
United States of America

AT THE SECOND SESSION

Begun and held at the City of Washington on Monday, the third day of January, two thousand and twenty-two

An Act

Making consolidated appropriations for the fiscal year ending September 30, 2023, and for providing emergency assistance for the situation in Ukraine, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Consolidated Appropriations Act, 2023".

SEC. 2. TABLE OF CONTENTS.

Sec. 1. Short title.
Sec. 2. Table of contents.
Sec. 3. References.
Sec. 4. Explanatory statement.
Sec. 5. Statement of appropriations.
Sec. 6. Adjustments to compensation.

DIVISION A—AGRICULTURE, RURAL DEVELOPMENT, FOOD AND DRUG ADMINISTRATION, AND RELATED AGENCIES APPROPRIATIONS ACT, 2023

Title I—Agricultural Programs
Title II—Farm Production and Conservation Programs
Title III—Rural Development Programs
Title IV—Domestic Food Programs
Title V—Foreign Assistance and Related Programs
Title VI—Related Agency and Food and Drug Administration
Title VII—General Provisions

DIVISION B—COMMERCE, JUSTICE, SCIENCE, AND RELATED AGENCIES APPROPRIATIONS ACT, 2023

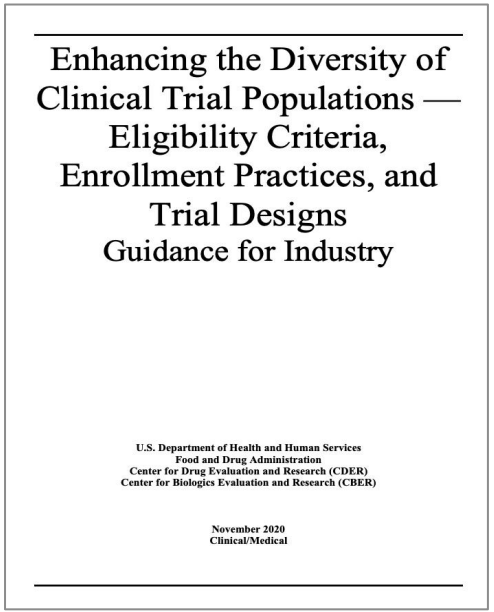
Title I—Department of Commerce
Title II—Department of Justice
Title III—Science
Title IV—Related Agencies
Title V—General Provisions

DIVISION C—DEPARTMENT OF DEFENSE APPROPRIATIONS ACT, 2023

Title I—Military Personnel
Title II—Operation and Maintenance
Title III—Procurement
Title IV—Research, Development, Test and Evaluation
Title V—Revolving and Management Funds
Title VI—Other Department of Defense Programs
Title VII—Related Agencies
Title VIII—General Provisions

DIVISION D—ENERGY AND WATER DEVELOPMENT AND RELATED AGENCIES APPROPRIATIONS ACT, 2023

Title I—Corps of Engineers—Civil
Title II—Department of the Interior
Title III—Department of Energy

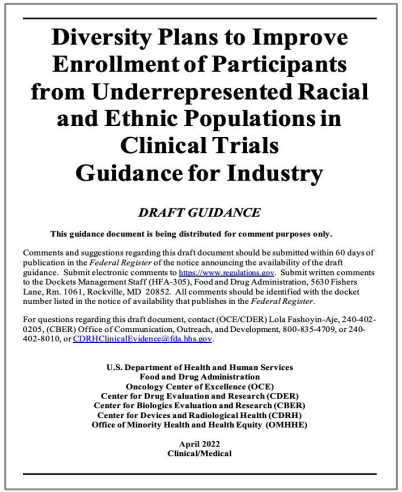


Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs

Guidance for Industry

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

November 2020
Clinical/Medical



Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (OCE/CDER) Lola Fashoyin-Aje, 240-402-0205, (CBER) Office of Communication, Outreach, and Development, 800-835-4709, or 240-402-8010, or CDRHClinicalEvidence@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Minority Health and Health Equity (OMHHE)

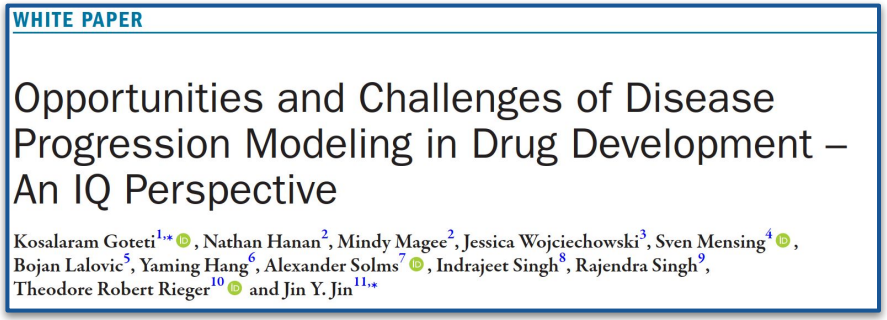
April 2022
Clinical/Medical

PAIN POINTS	OPPORTUNITIES
Delayed patient access due to difficulties enrolling a diverse population in the US	• **Leverage data from global population as appropriate**
Insufficient understanding of differential drug effects across populations	• **Develop standards and path for reporting population-specific variations in safety, efficacy and dosing**

Emerging Methodologies: Disease Progression Modeling (DPM)

Opportunities for Regulatory Action & Guidance to Advance Innovation

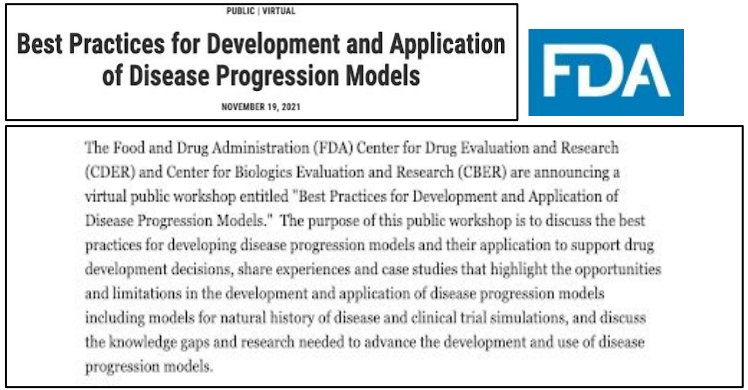
2021 Survey from 16 Companies[1]



WHITE PAPER

Opportunities and Challenges of Disease Progression Modeling in Drug Development – An IQ Perspective

Kosalaram Goteti[1,*], Nathan Hanan[2], Mindy Magee[2], Jessica Wojciechowski[3], Sven Mensing[4], Bojan Lalovic[5], Yaming Hang[6], Alexander Solms[7], Indrajeet Singh[8], Rajendra Singh[9], Theodore Robert Rieger[10] and Jin Y. Jin[11,*]



PUBLIC | VIRTUAL

Best Practices for Development and Application of Disease Progression Models

NOVEMBER 19, 2021

FDA

The Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) are announcing a virtual public workshop entitled "Best Practices for Development and Application of Disease Progression Models." The purpose of this public workshop is to discuss the best practices for developing disease progression models and their application to support drug development decisions, share experiences and case studies that highlight the opportunities and limitations in the development and application of disease progression models including models for natural history of disease and clinical trial simulations, and discuss the knowledge gaps and research needed to advance the development and use of disease progression models.

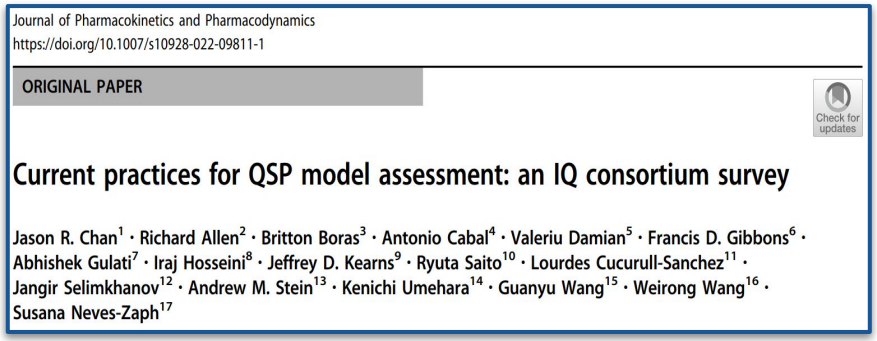
PAIN POINTS	OPPORTUNITIES
"Lack of clear regulatory guidance and path"	• **Guidance and regulatory path for how to apply and communicate disease model integration knowledge and data from multiple molecules**
"Lack of impact showcase, especially for regulatory acceptance"	• **Organization and promotion of impact showcase, especially in the context of regulatory decision support**
"Non-competitive data and model sharing"	• **Advocate and support (eg. with non-profit organizations) for data and model sharing and endorsement of mature models/tools**

[1] Goteti K, et al. Opportunities and Challenges of Disease Progression Modeling in Drug Development - An IQ Perspective. *Clin Pharmacol Ther.* 2023. 114(2):266-274

Emerging Methodologies: Quantitative System Pharmacology (QSP)

Opportunities for Regulatory Action & Guidance to Advance Innovation

2021 Survey from 23 Companies[1]



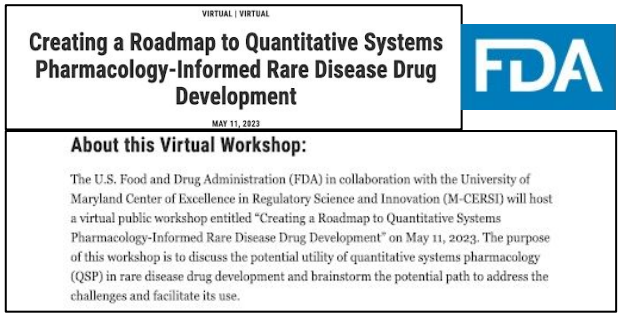
Journal of Pharmacokinetics and Pharmacodynamics
https://doi.org/10.1007/s10928-022-09811-1

ORIGINAL PAPER

Check for updates

Current practices for QSP model assessment: an IQ consortium survey

Jason R. Chan[1] · Richard Allen[2] · Britton Boras[3] · Antonio Cabal[4] · Valeriu Damian[5] · Francis D. Gibbons[6] · Abhishek Gulati[7] · Iraj Hosseini[8] · Jeffrey D. Kearns[9] · Ryuta Saito[10] · Lourdes Cucurull-Sanchez[11] · Jangir Selimkhanov[12] · Andrew M. Stein[13] · Kenichi Umehara[14] · Guanyu Wang[15] · Weirong Wang[16] · Susana Neves-Zaph[17]



VIRTUAL | VIRTUAL

Creating a Roadmap to Quantitative Systems Pharmacology-Informed Rare Disease Drug Development

MAY 11, 2023

FDA

About this Virtual Workshop:

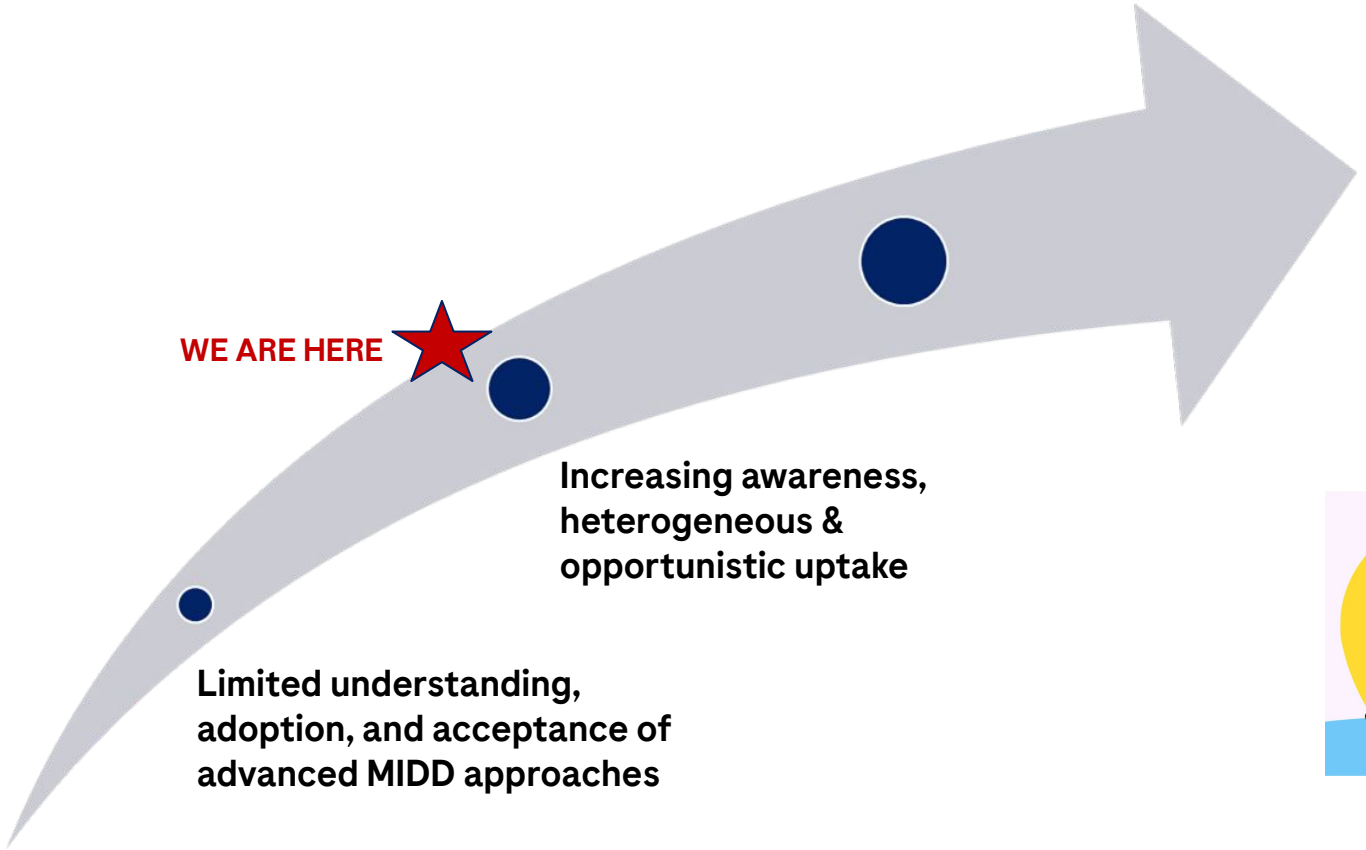
The U.S. Food and Drug Administration (FDA) in collaboration with the University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI) will host a virtual public workshop entitled "Creating a Roadmap to Quantitative Systems Pharmacology-Informed Rare Disease Drug Development" on May 11, 2023. The purpose of this workshop is to discuss the potential utility of quantitative systems pharmacology (QSP) in rare disease drug development and brainstorm the potential path to address the challenges and facilitate its use.

PAIN POINTS	OPPORTUNITIES
"The use of QSP modeling to support regulatory interactions appears to be infrequent" *Apparent disconnect between IQ survey & FDA report[2]*	• **Organization and promotion of sharing specific impact showcase, especially in the context of regulatory decision support**
"Model assessment appears to be quite variable" *"standardization of approaches towards virtual populations"* *"Documentation of QSP models"*	• **Regulatory Guidance especially for model assessment & reporting** • ***"The risk-based framework for verification and validation (proposed by FDA) can be applied although the details need to be carefully considered given that few QSP projects are alike."***

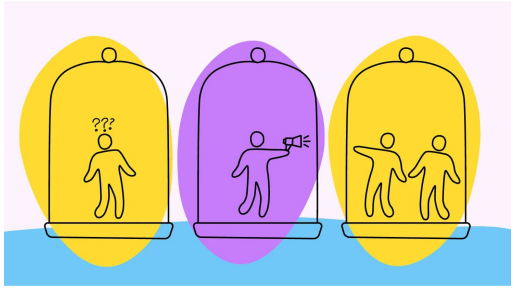
[1] Chan JR, et al. Current practices for QSP model assessment: an IQ consortium survey. *J Pharmacokinet Pharmacodyn.* 2022. 11:1–13
[2] Bai JPF, et al. Quantitative systems pharmacology: landscape analysis of regulatory submissions to the US Food and Drug Administration. *CPT Pharmacometrics Syst Pharmacol.* 2021. 10(12):1479–1484

Call to Action: Advance Innovation at Scale

Moving from Pilots to Practice



Break down the silos!



Doing now what patients need next