# The Quantitative and the Mechanistic: Strategies to Advance Rare Disease Drug Development Through Regulatory Science

**Issam Zineh, PharmD, MPH, FCP, FCCP**

Director, Office of Clinical Pharmacology

Office of Translational Sciences

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

CERSI
University of Maryland

# Model-informed Drug Development (MIDD)

**Development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources to address drug development or regulatory issues**
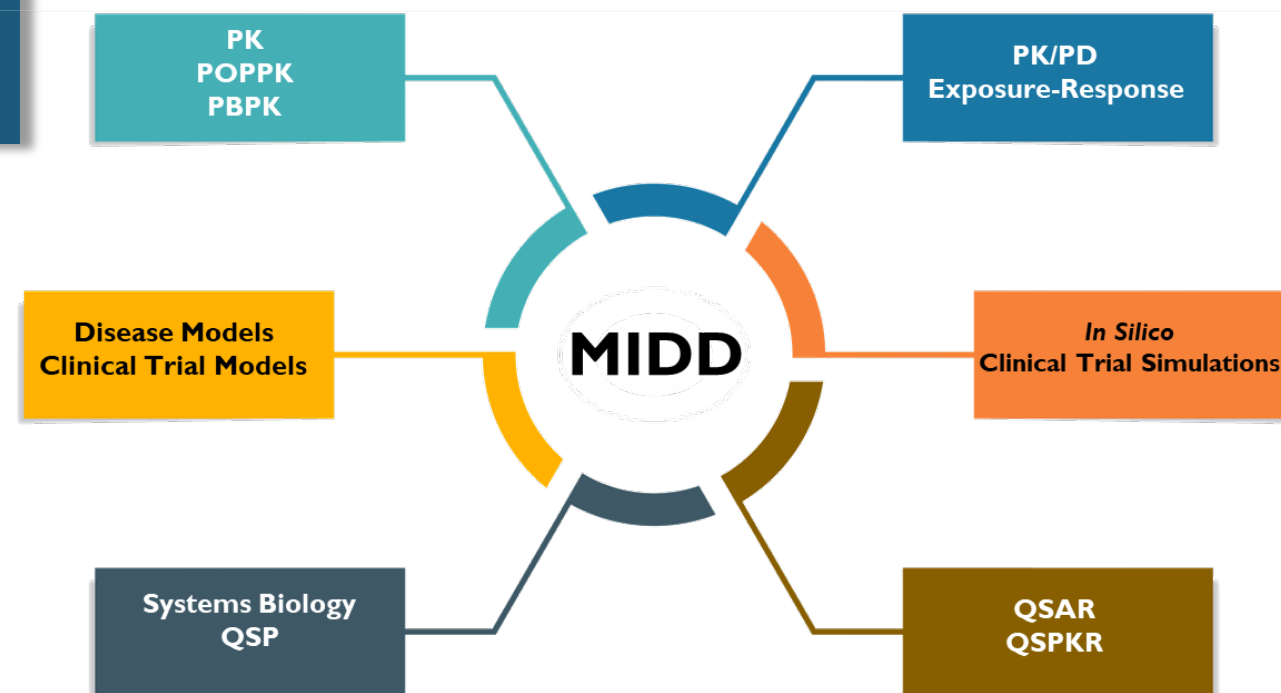
# Modeling & Simulation on the Critical Path

Recognized pathway to lower drug attrition, streamline development, and address regulatory uncertainty



**Problem Statement**:
Opportunistically applied, heterogeneously accepted, no dedicated pathways for engagement

# MIDD: Hope or Hype?
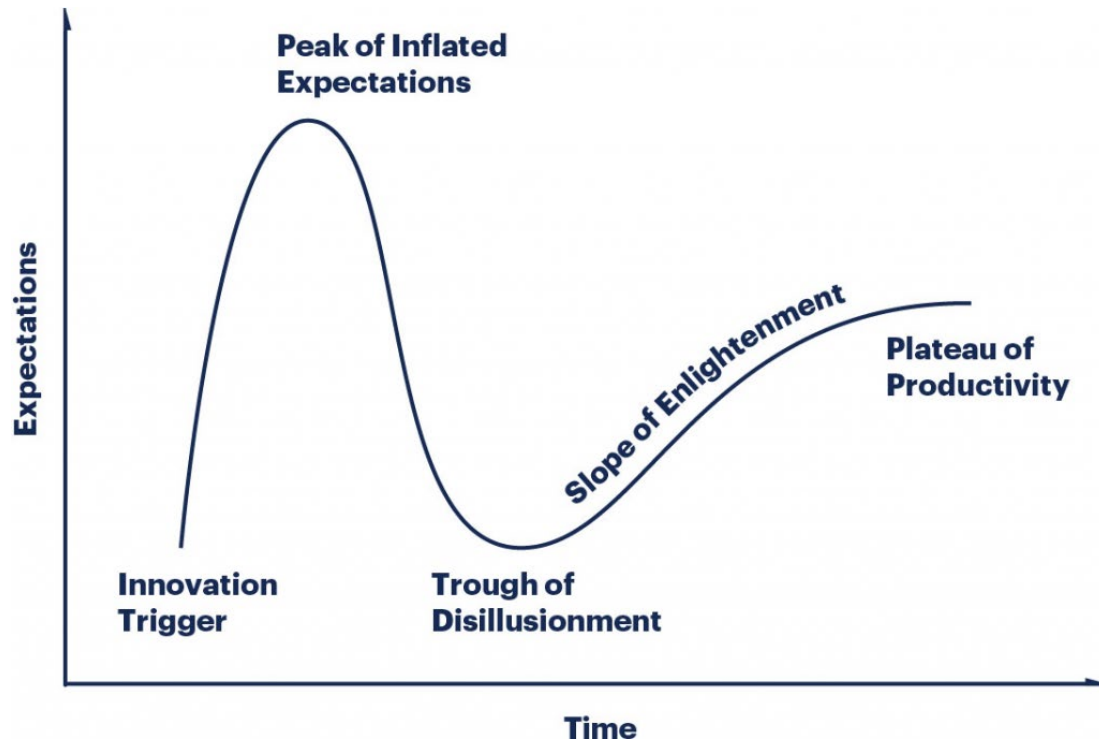
**MIDD & QSP in the Literature**
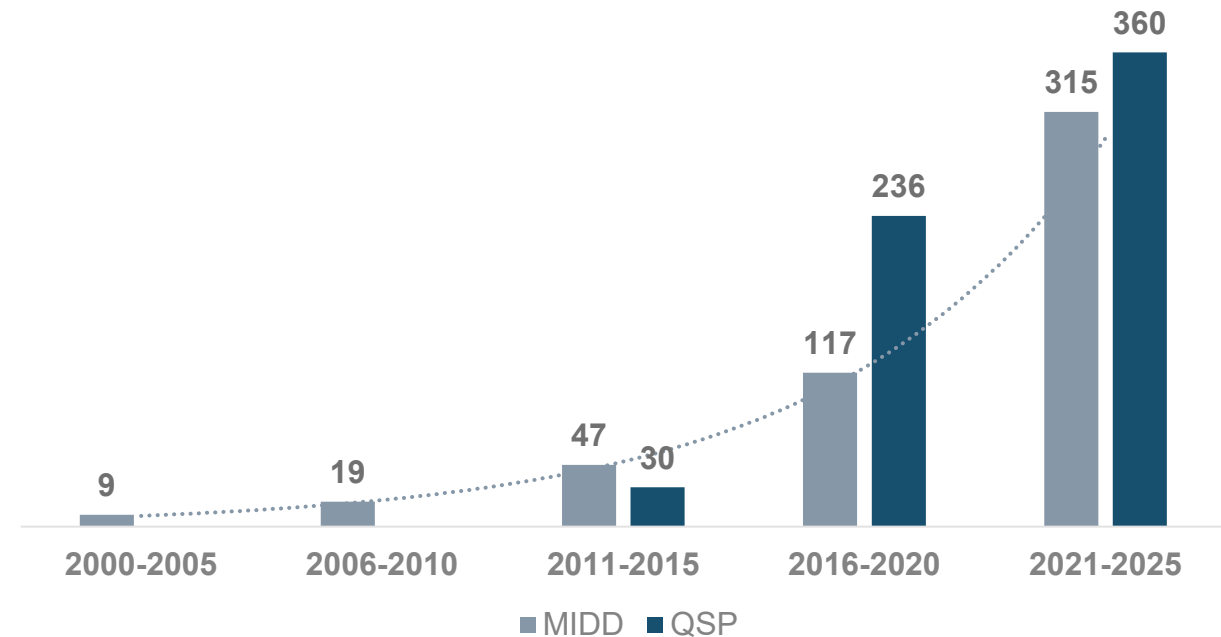
# Is QSP Exceptional?

## Historical Barriers to Translation

▶ Constraints of the science

▶ Steep learning curve among non-technical experts

▶ Few instructive cases

▶ High organizational activation energy



Legend:
- ■ E/R Modeling
- ○ Precision Medicine/Pgx
- ◇ PBPK
- ----- QSP Trajectory

Y-axis: Expectations

X-axis stages: Innovation Trigger | Peak of Inflated Expectations | Trough of Disillusionment | Slope of Enlightenment | Plateau of Productivity

**Stage of Hope-Hype Lifecycle**
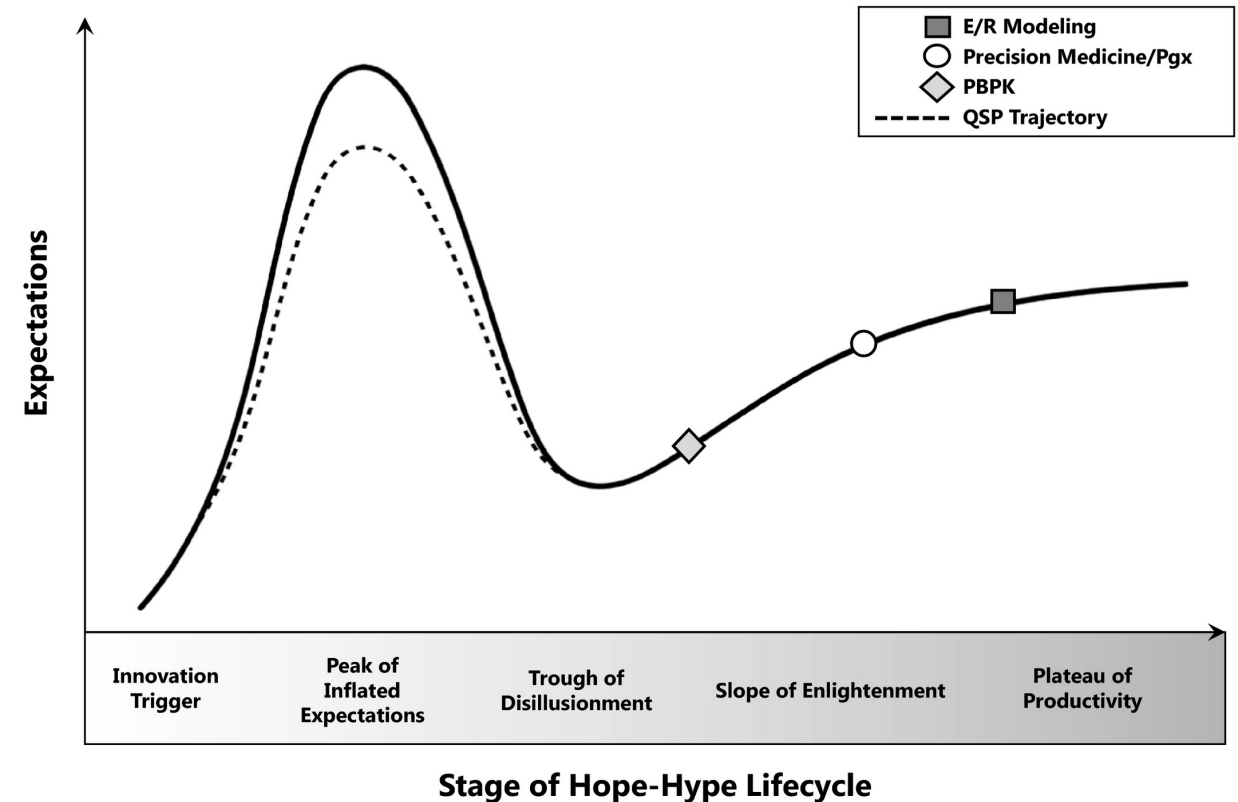
Regulatory Decision Tools: Rare Diseases

PDUFA VI — The Prescription Drug User Fee Act

2018-2022

Patient Voice
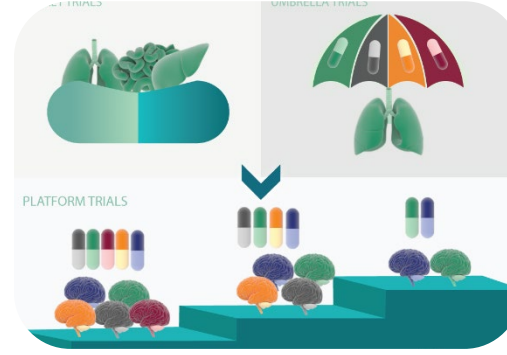
Complex Innovative Trial Designs
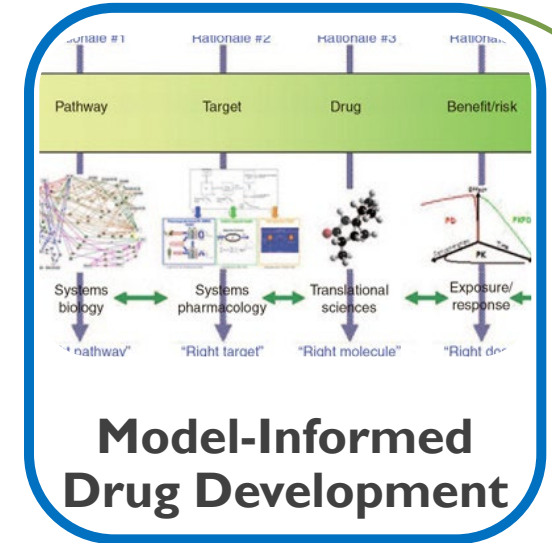
Model-Informed Drug Development

Analysis Data Standards
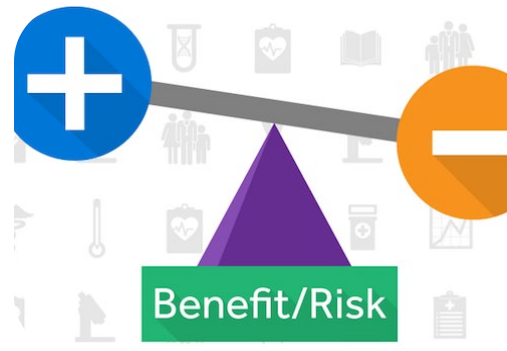
Benefit/Risk Assessment

Biomarker Qualification

# A Holistic and Integrative Approach for Advancing Model-Informed Drug Development

Rajanikanth Madabushi[1,*], Yaning Wang[1] and Issam Zineh[1]

1. Creating an environment that increases stakeholder acceptance of MIDD approaches

2. Developing standards and best practices that lead to consistent application and evaluation

3. Increasing capacity and expertise to address growing demands and innovation



Regulatory Science Capacity

Regulatory Review Capacity and Expertise

Guidance, MaPPs, SOPs, Review Tools

Stakeholder Engagement

MIDD Paired Meeting Pilot Program

Knowledge Management and Communication

# MIDD Paired Meeting Program
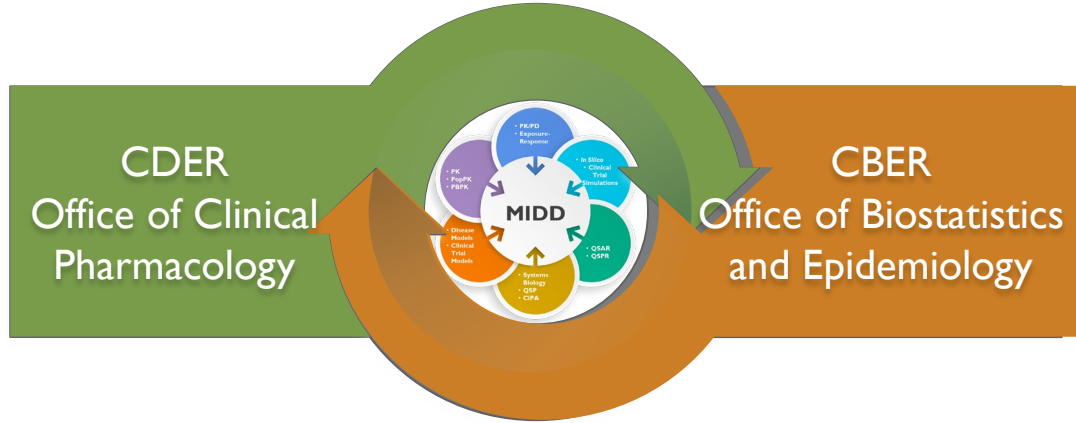
# Impact
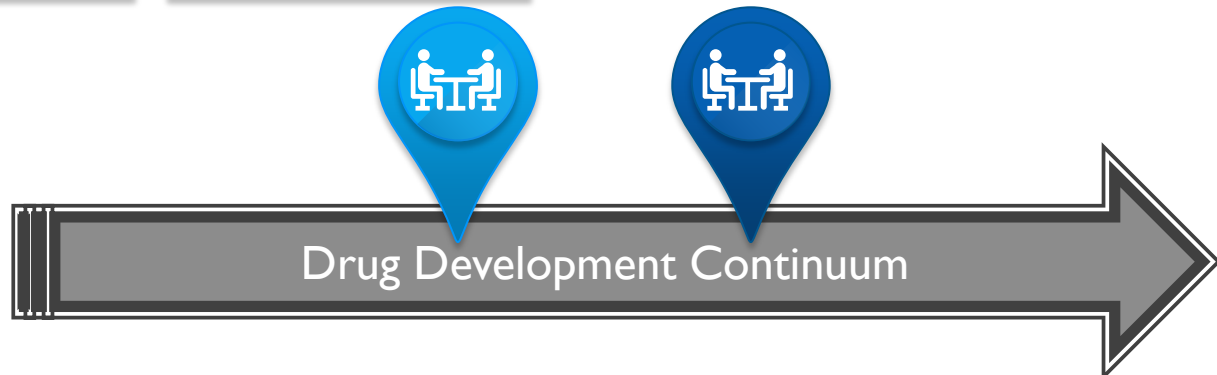
## Drug Development

**Model validation & clinical trial simulation to inform trial design and patient selection**

**Strategies for dose selection, optimization and risk mitigation**

**Alternative approaches for therapeutic individualization**

**Regulatory pathway seeking approval of new dose, dosing regimen, formulation, etc.**

### TIME
- Accelerated timelines
- Reduced sample size, faster recruitment
- Getting to right dose faster

### COST
- Savings est. up to $70M
- M/S replacing trials
- Path to potential new indications

### ALIGNMENT
- Study design
- Modeling approach
- Technical feasibility
- Traction gained

### CLARITY
- Direct feedback
- Technical expectations
- Additional data needs
- Engaged scrutiny

# QSP Submissions

**CLINICAL TRIAL PLANNING**

- Patient Selection
- Dose Selection
- Response Measure Selection
- Trial Duration

**QSP**

**Knowledge Model**

**+**

**Computational Model**

**DECISION**

- Development Trajectory
- Regulatory Action

# QSP Submissions

**KNOWLEDGE MODEL**

▶ Model breadth (pathophysiology; PK; pharmacology/target engagement ▶ biology/physiology ▶ clinical outcomes)

▶ Literature/experimental knowledge ▶ assertions

▶ Objective strength-of-evidence

▶ Transparency in addressing uncertainty

Transparency and traceability ◀

Calibration ◀

Validation plan (+ code/calculation verification) ◀

**COMPUTATIONAL MODEL**

# What is the Question?

**Risk-Informed Credibility Assessment**

- Question of Interest
- Context of Use
- Model Influence
- Decision Consequence

Standardizes terminology and streamlines assessment

Aids in communication and increase transparency

De-risks and advances MIDD applications

Kuemmel *et al* 2020 PMID: 31652029;  Viceconti *et al* 2020 PMID: 31991193
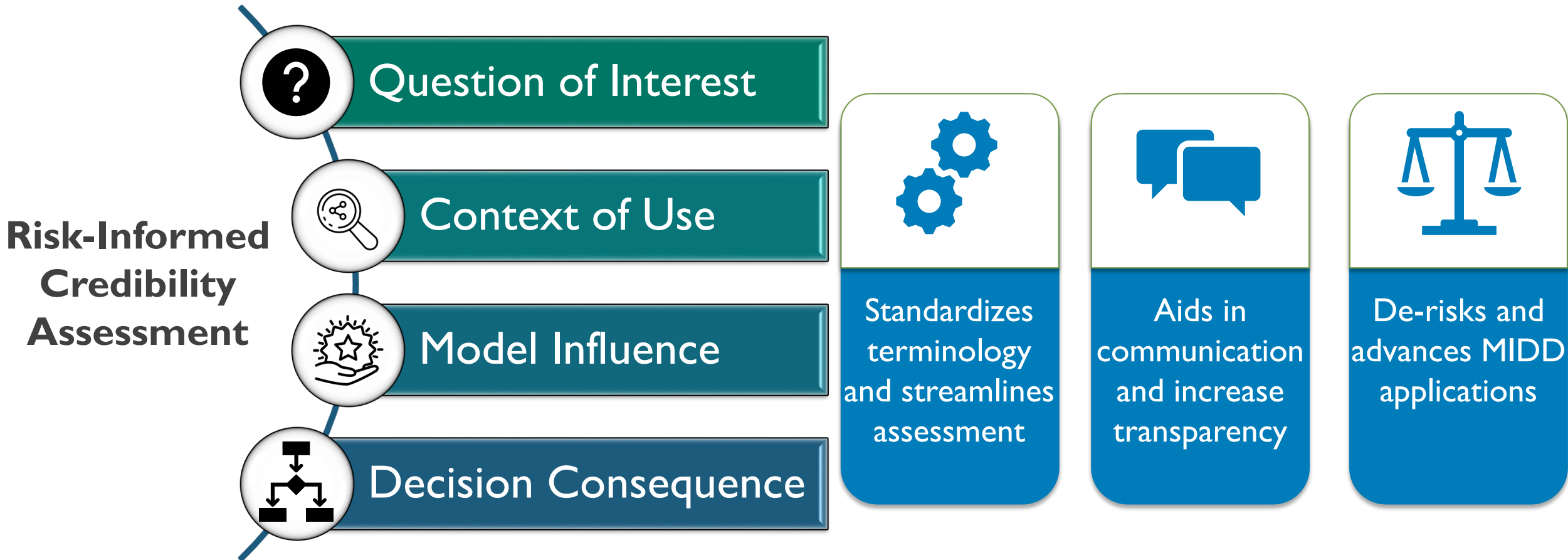
# Model Risk Drives Validation/Verification Discussions

**Model Influence**

**Decision Consequence**

**Future Model Use**
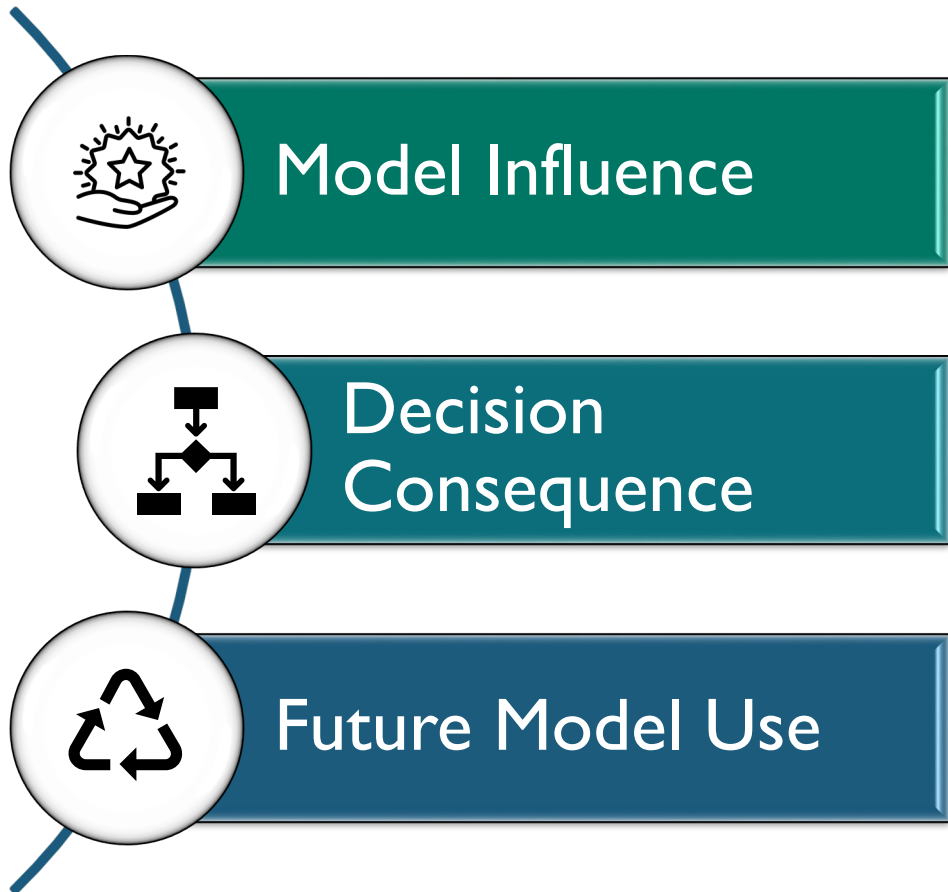
▶ What does the model reproduce?

– Measures of target engagement

– Biological activity

– Intermediate clinical outcomes

– Clinical outcomes

– Dose-response

▶ In what population?

– In vivo animal

– Human, disease-analogous

– Human, disease of interest

# What's Next for QSP?

"The biggest return on investment for QSP is likely in drug discovery and development…as a result, we might hypothesize that the success of QSP in therapeutic product development will be largely…driven by pharmaceutical company capability and acceptance, as opposed to regulatory acceptance….

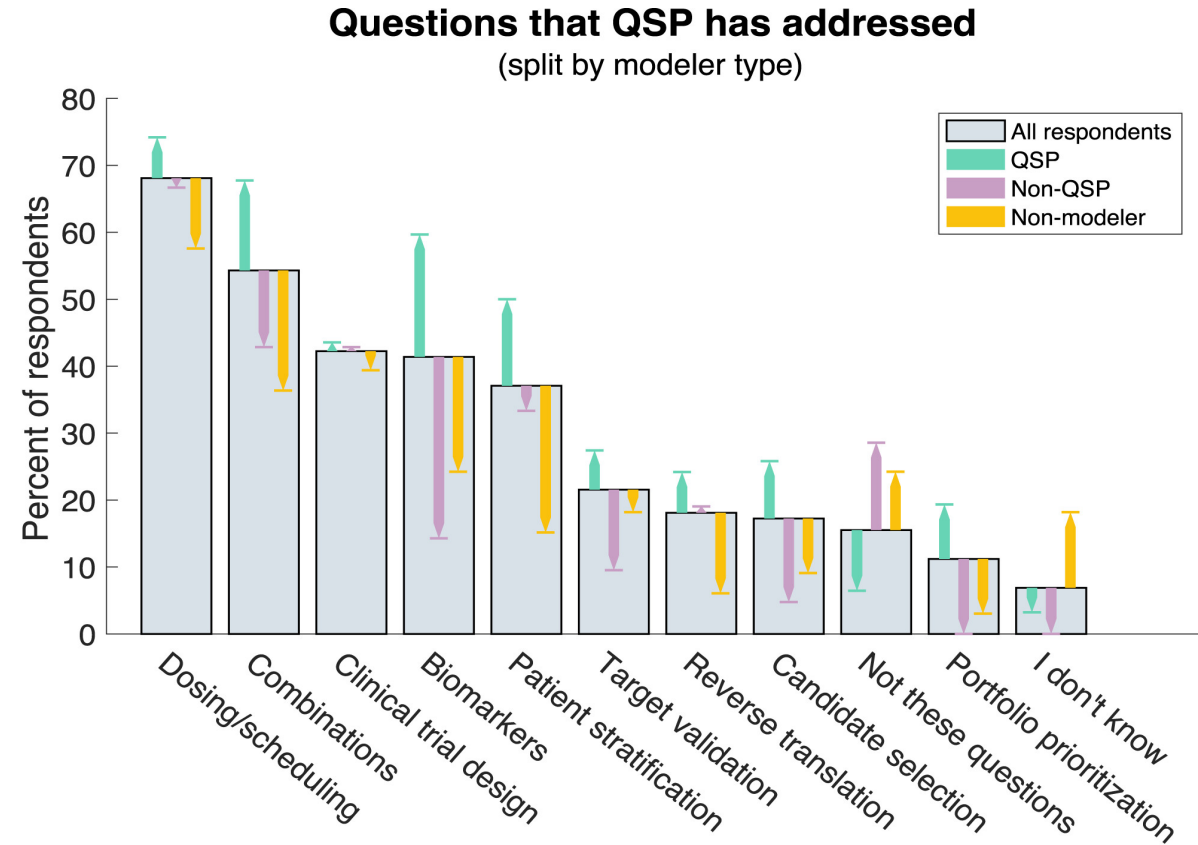[T]he important question around the role of regulatory scientists in evaluating QSP models and output in regulatory decision making should be publicly discussed…

[T]he role of academic researchers should not be underestimated given that the strength of the mechanistic knowledge base that drives QSP is dependent on basic, translational, and clinical research performed in academic research environments."

# The Opportunity Space for Rare Diseases

## Potential QSP Applications…

▶ Clinical Trial Design
  – Patient selection/enrichment, trial duration

▶ Dose selection/optimization

▶ Biomarker selection
  – Dose-/time-dependency
  – Biomarker dynamics in target tissues
  – Relationship to clinical outcomes

▶ Strength of hypothesis

▶ Mechanistically-informed safety assessment

▶ Extrapolation

▶ "Reverse translation" – understanding response variability (differential D/R; differential outcomes)



**Questions that QSP has addressed**
(split by modeler type)

Legend: All respondents, QSP, Non-QSP, Non-modeler

Lemaire 2022 [PMID 36282521]

# The Opportunity Space for Rare Diseases



**Challenges of QSP**
(split by modeler type)

Legend:
- All respondents
- QSP
- Non-QSP
- Non-modeler

Y-axis: Percent of respondents (0–80)

X-axis categories:
- Not enough data
- Timeline is too long
- Lacking validation
- Low engagement
- Insufficient resources
- Too complicated
- Budget is too high
- Not needed
- I don't know
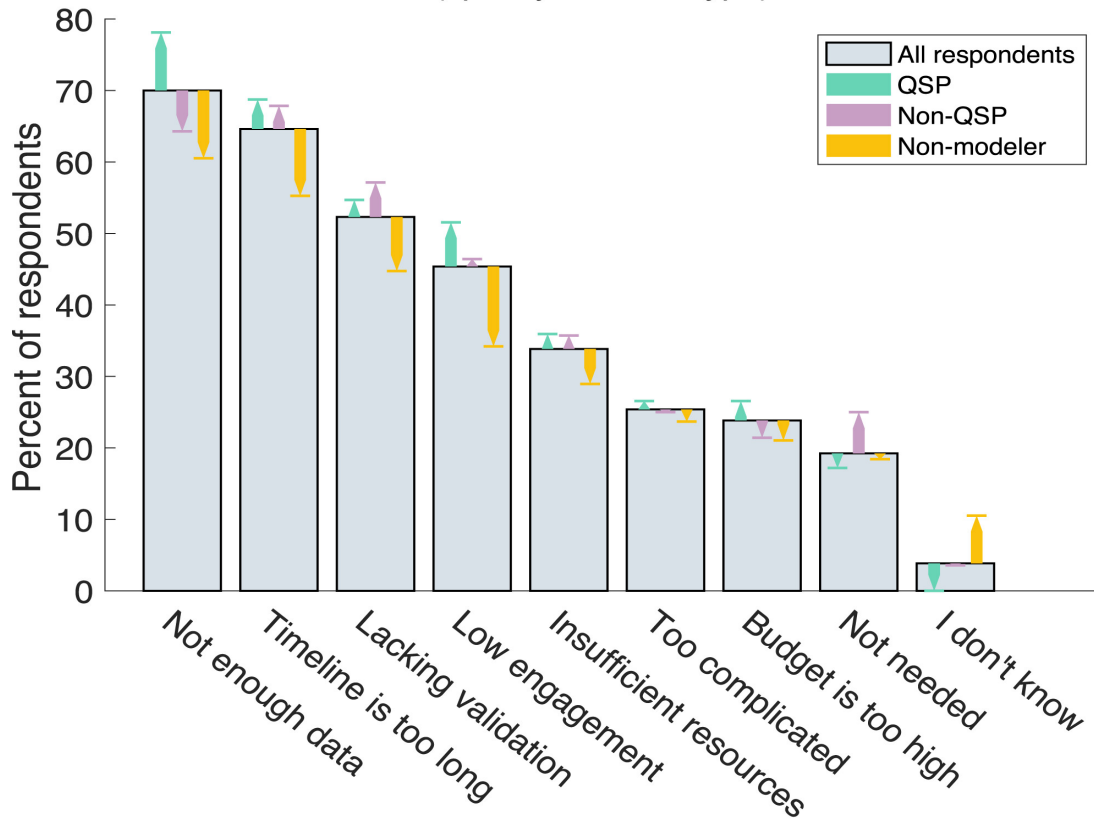
## QSP Regulatory Challenges…

▶ Extensive literature review

▶ Paucity of domain expertise

▶ Timeline mismatch

▶ QSP model validation standards

# Summary & Conclusions

- MIDD has matured and is enjoying routine application
- Greater openness to a variety of M&S strategies, including mechanistic (e.g., QSP)
- QSP most routinely applied in clinical trial planning
- Clarity on QOI/COU is critical to discussions around whether QSP model is fit for its intended use
- Challenges inherent in rare disease drug development make mechanistic approaches desirable
- A broad opportunity space exists, but a variety of current challenges (not specific to rare diseases) must continue to be addressed