

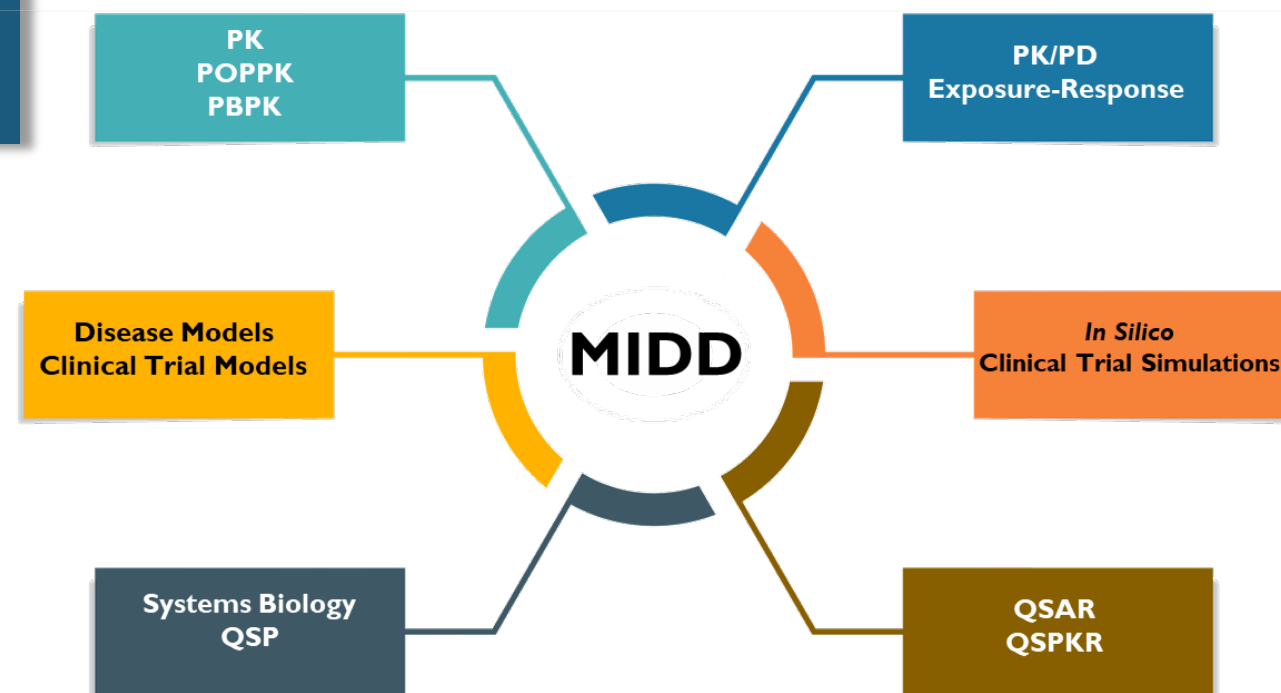
The Quantitative and the Mechanistic: Strategies to Advance Rare Disease Drug Development Through Regulatory Science



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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




How FDA Plans to Help Consumers Capitalize on Advances in Science

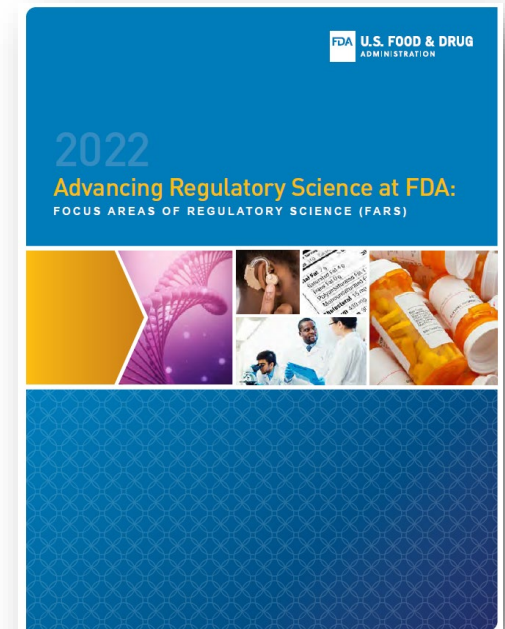
Posted on July 7, 2017 by FDA Voice

By: Scott Gottlieb, M.D.

We're at a point in science where new medical technologies hold out the promise of better treatments for a widening number of vexing conditions. Over the last few decades, science has enabled fundamental advances in our understanding of the genetic and protein bases of human disease. These developments are already being translated into new medicines. In more cases, these treatments target the underlying mechanisms that drive different diseases. These advances hold out the promise of arresting and even curing a growing number of diseases.



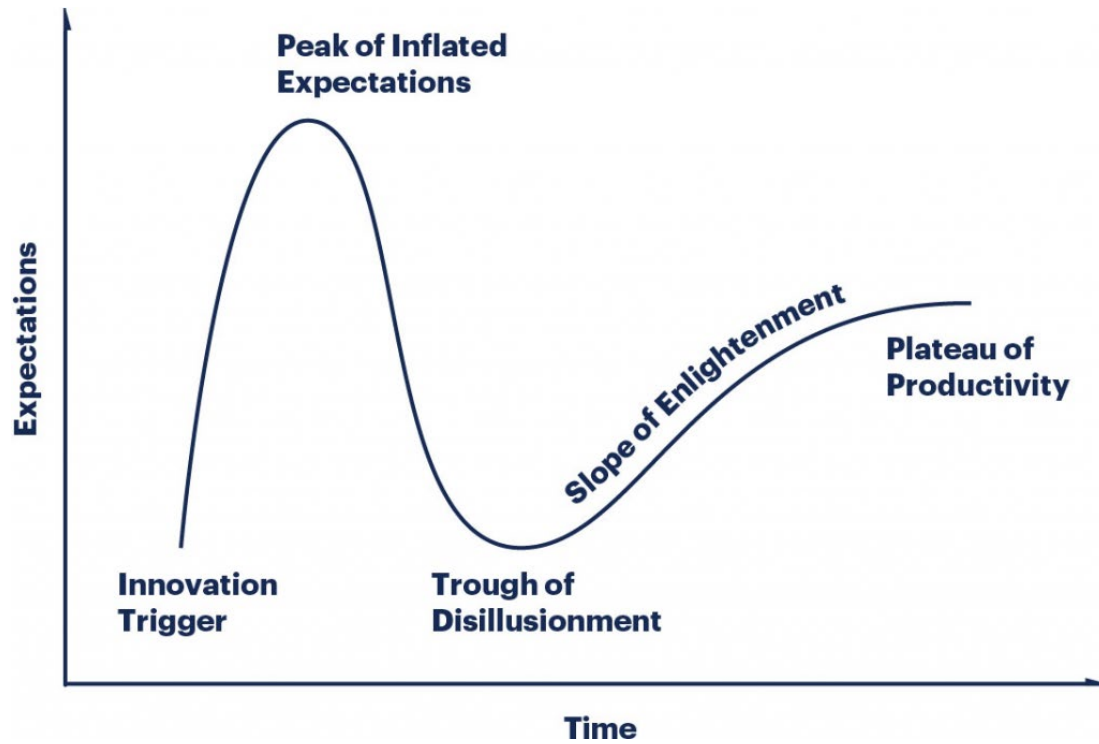
To build upon such opportunities, FDA will soon unveil a comprehensive Innovation Initiative. It will be aimed at making sure our regulatory processes are modern and efficient, so that safe and effective new technologies can reach patients in a timely fashion. We need to make sure that our regulatory principles are efficient and informed by the most up to date science. We don't want to present regulatory barriers to beneficial new medical innovations that add to the time, cost, and uncertainty of bringing these technologies forward if they don't add to our understanding of the product's safety and benefits.



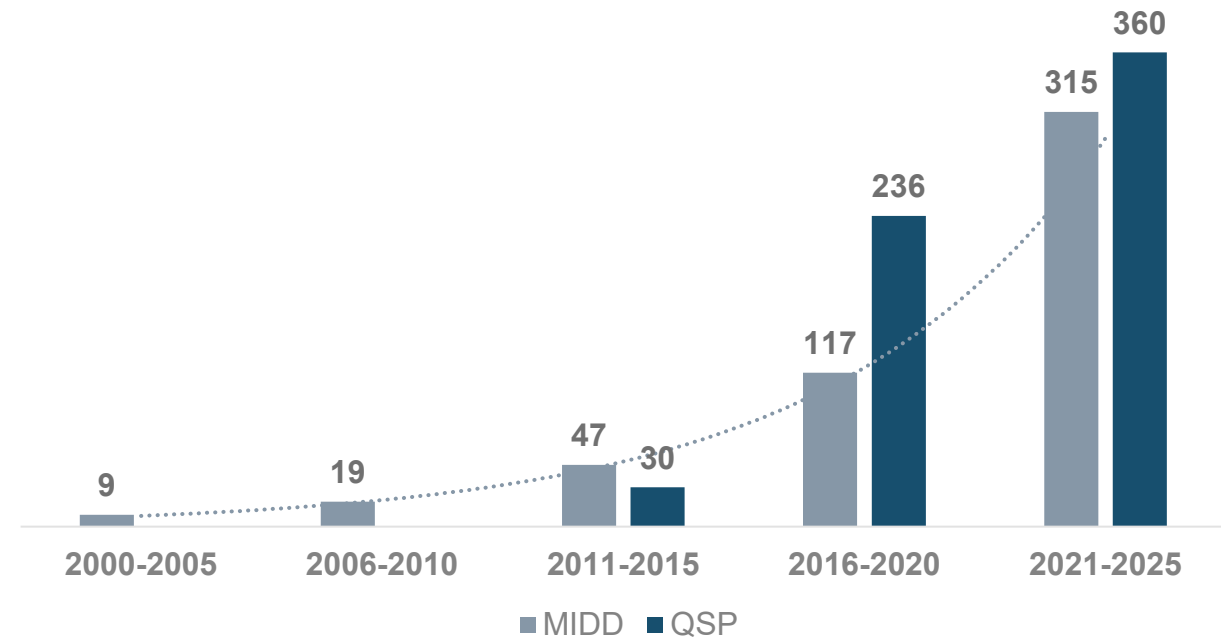
Problem Statement:

Opportunistically applied, heterogeneously accepted, no dedicated pathways for engagement

MIDD: Hope or Hype?



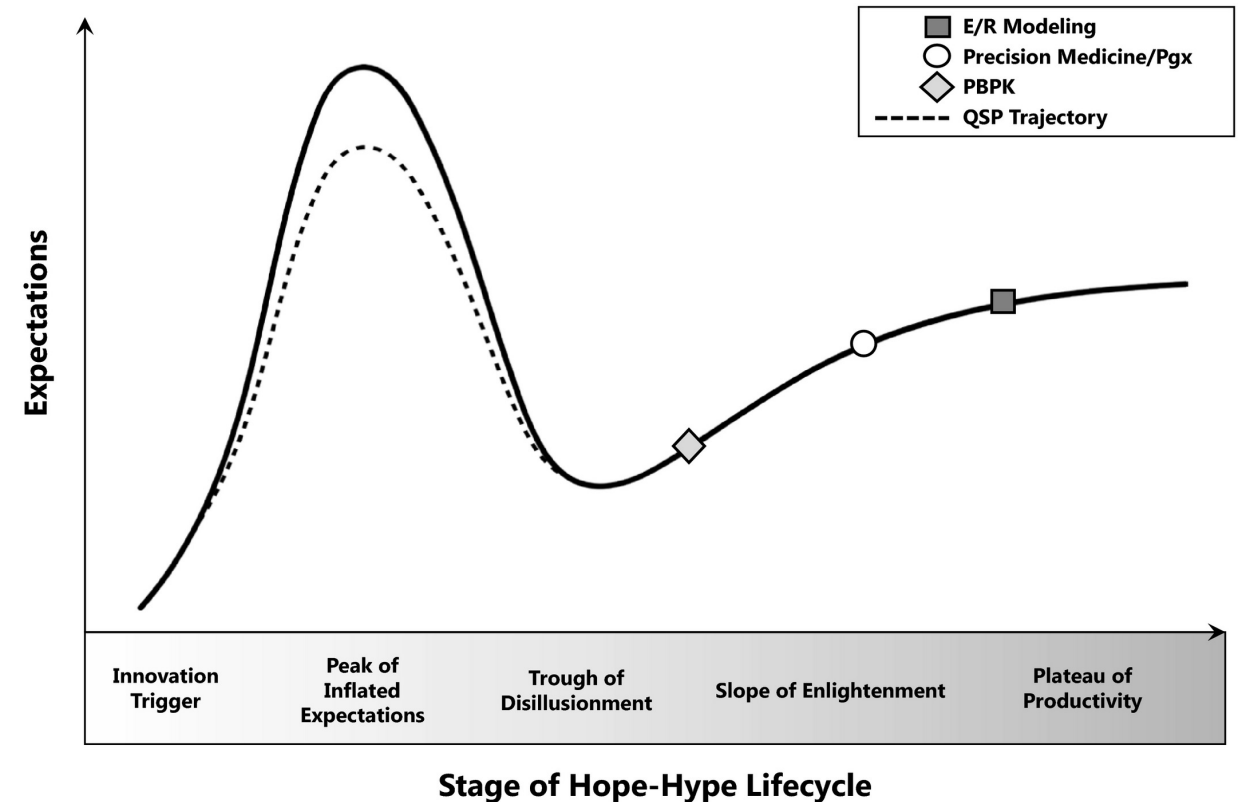
MIDD & QSP in the Literature



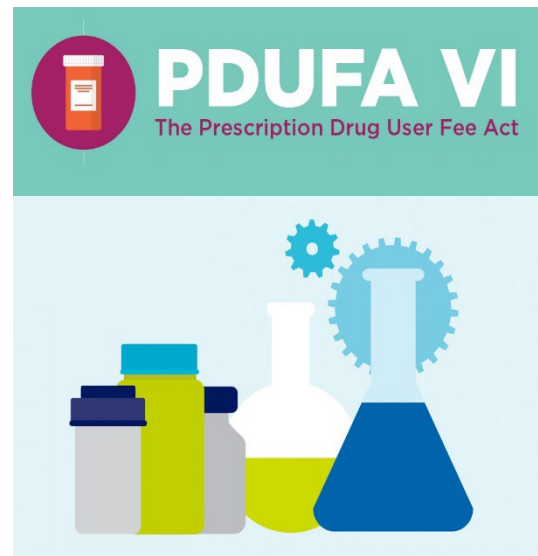
Is QSP Exceptional?

Historical Barriers to Translation

- ▶ Constraints of the science
- ▶ Steep learning curve among non-technical experts
- ▶ Few instructive cases
- ▶ High organizational activation energy



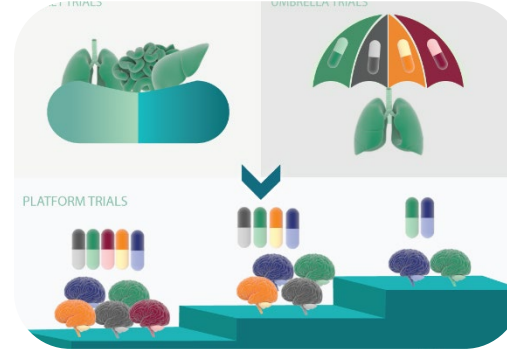
Regulatory Decision Tools: Rare Diseases



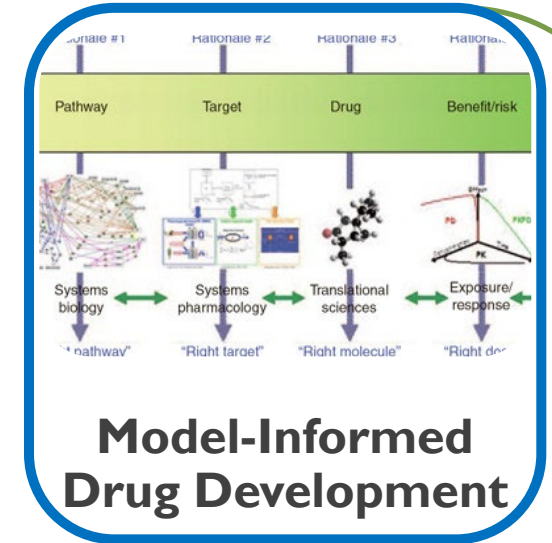
2018-2022



Patient Voice



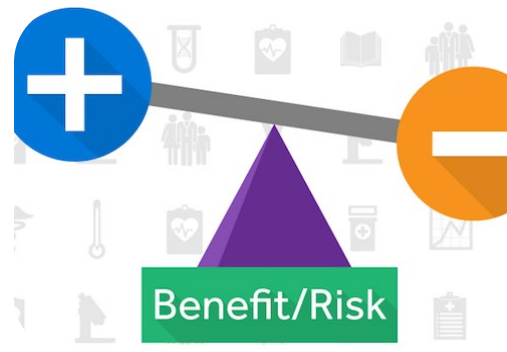
Complex Innovative Trial Designs



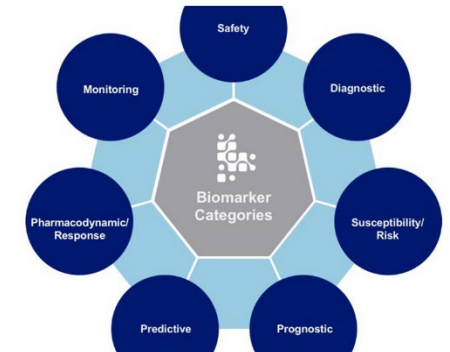
Model-Informed Drug Development



Analysis Data Standards



Benefit/Risk Assessment



Biomarker Qualification

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

Rajanikanth Madabushi^{1,*}, Yaning Wang¹ and Issam Zineh¹

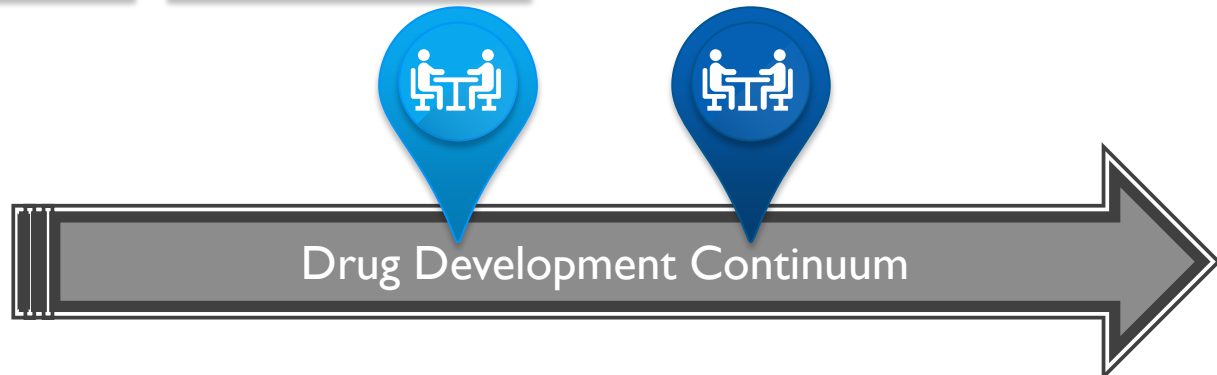
- 1 Creating an environment that increases stakeholder acceptance of MIDD approaches
- 2 Developing standards and best practices that lead to consistent application and evaluation
- 3 Increasing capacity and expertise to address growing demands and innovation



MIDD Paired Meeting Program



A dedicated forum for regulatory interaction on MIDD applications in specific drug development programs



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



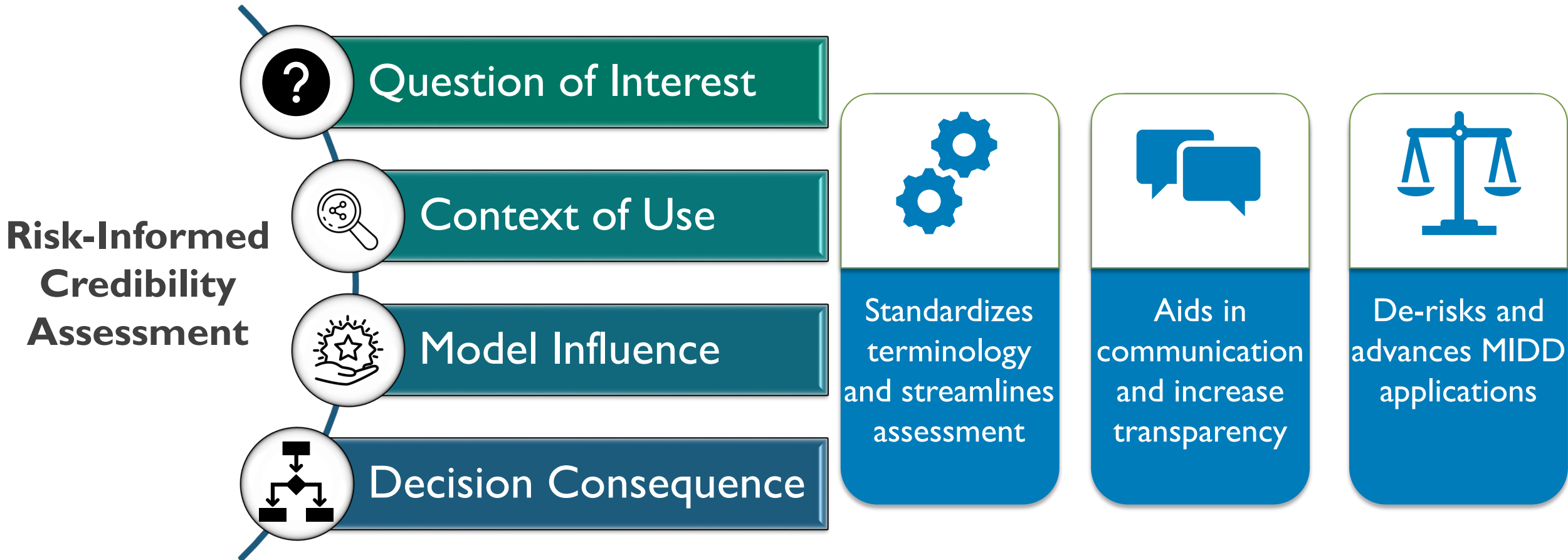
Transparency and traceability

Calibration

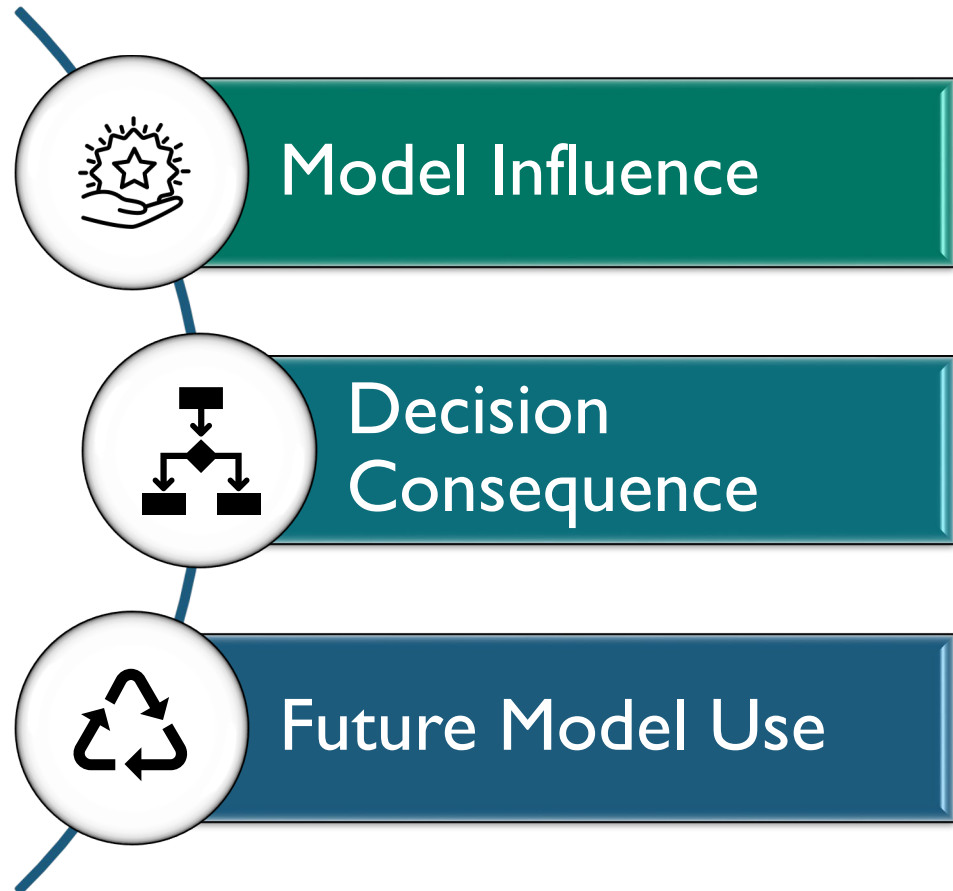
Validation plan
(+ code/calculation verification)

COMPUTATIONAL MODEL

What is the Question?



Model Risk Drives Validation/Verification Discussions



- ▶ 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....

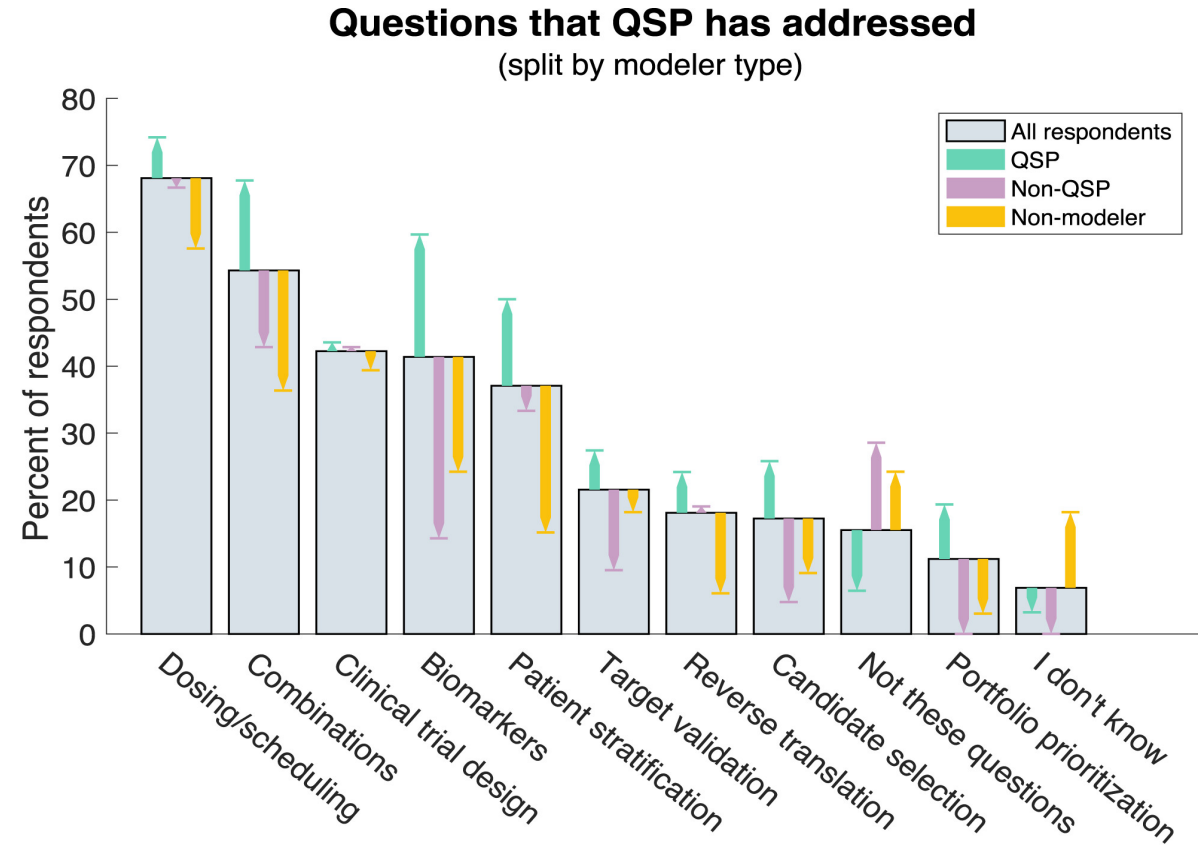
[T]he important question around the role of regulatory scientists in evaluating QSP models and output in regulatory decision making should be publicly discussed...

[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

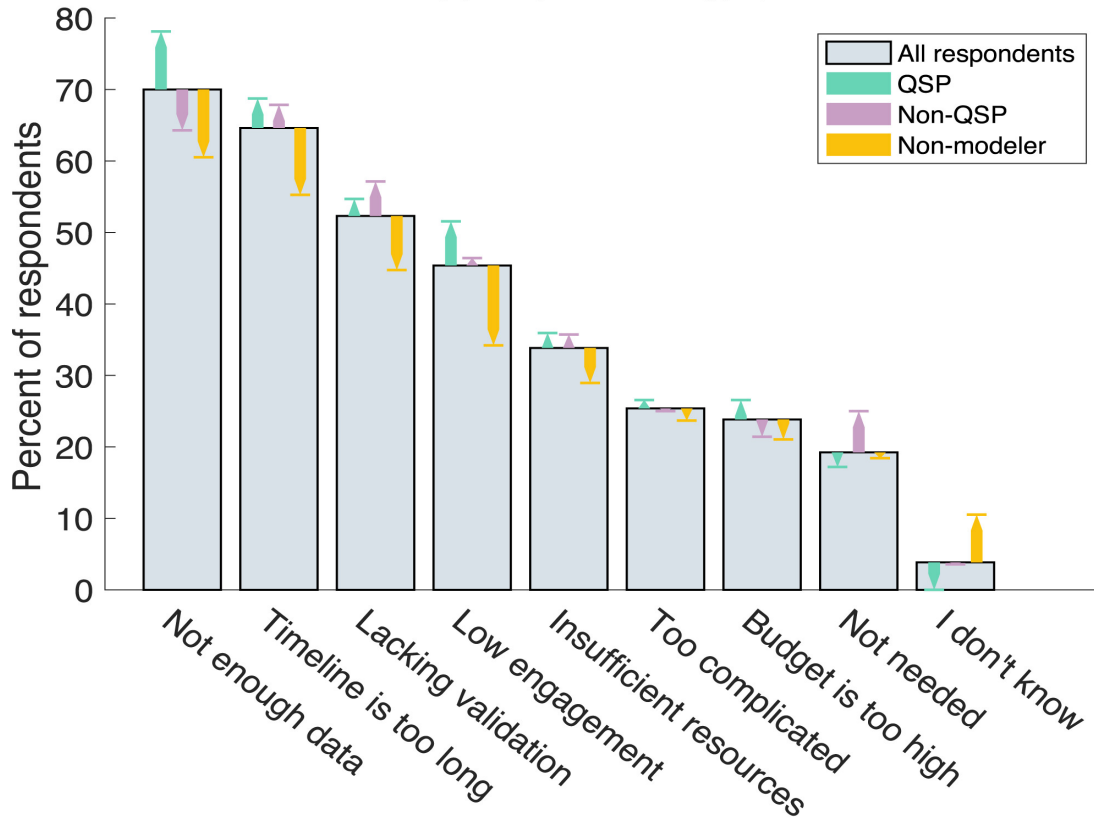
Potential QSP Applications...

- ▶ 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)



The Opportunity Space for Rare Diseases

Challenges of QSP
(split by modeler type)



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