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ASCPT 2019
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Quantitative Systems Pharmacology at the US FDA: From Aspiration to Translation

Issam Zineh, PharmD, MPH

Office of Clinical Pharmacology | Office of Translational Sciences

US Food and Drug Administration | March 13, 2019

Acknowledgments

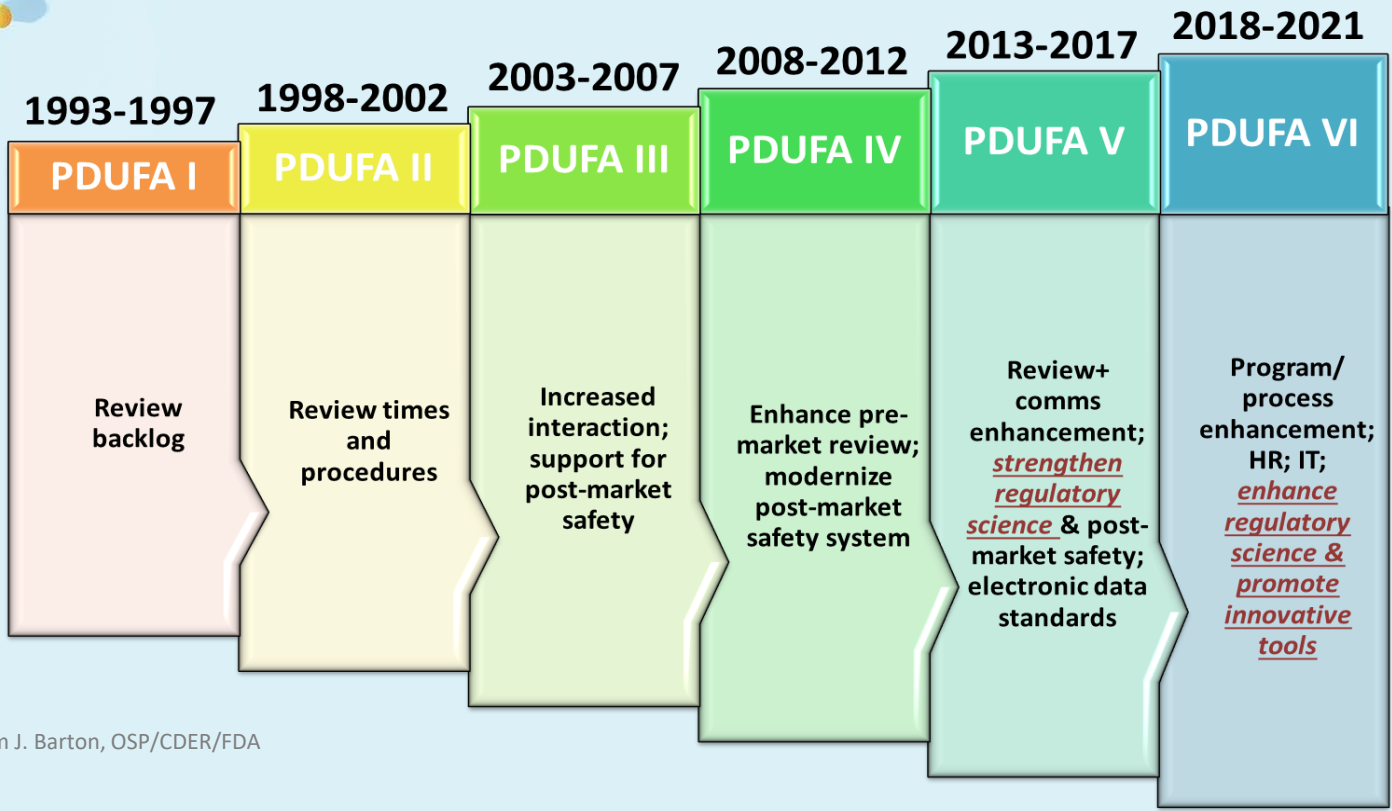
- Drs. Jane Bai, Kimberly Bergman, Jeffry Florian, Shiew Mei Huang, Colleen Kuemmel, Zihua Li, Rajnikanth Madabushi, Michael Pacanowski, and Yanning Wang
- Editors of CPT:PSP: Zineh I. Quantitative Systems Pharmacology: A Regulatory Perspective on Translation [Accepted]
- The views expressed are mine and may not reflect the position of the US Food and Drug Administration. No official position is intended nor should be inferred.

Overview

- Current MIDD Landscape
- Pattern Recognition: QSP on the Regulatory Hope-Hype Cycle
- Setting Expectations
 - Reflections on the Community
 - QSP Submissions at FDA
- Outstanding Questions
- Summary

Increased Focus on Innovation, Novelty, and Advancing Regulatory Science

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Modified from J. Barton, OSP/CDER/FDA

Opportunities for MIDD: PDUFA VI – Enhancing Regulatory Decision Tools To Support Drug Development and Review

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**Regulatory Science
Capacity**



**Regulatory Review
Capacity and Expertise**



**Guidance, MaPPs,
SOPs, Review Tools**



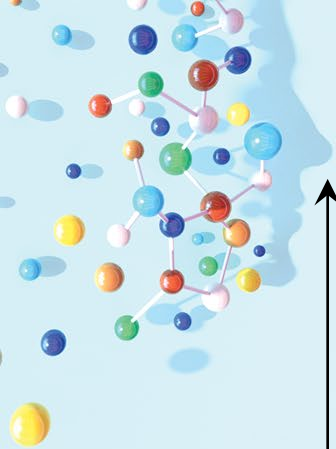
**Stakeholder
Engagement**



**MIDD Paired Meeting
Pilot Program**

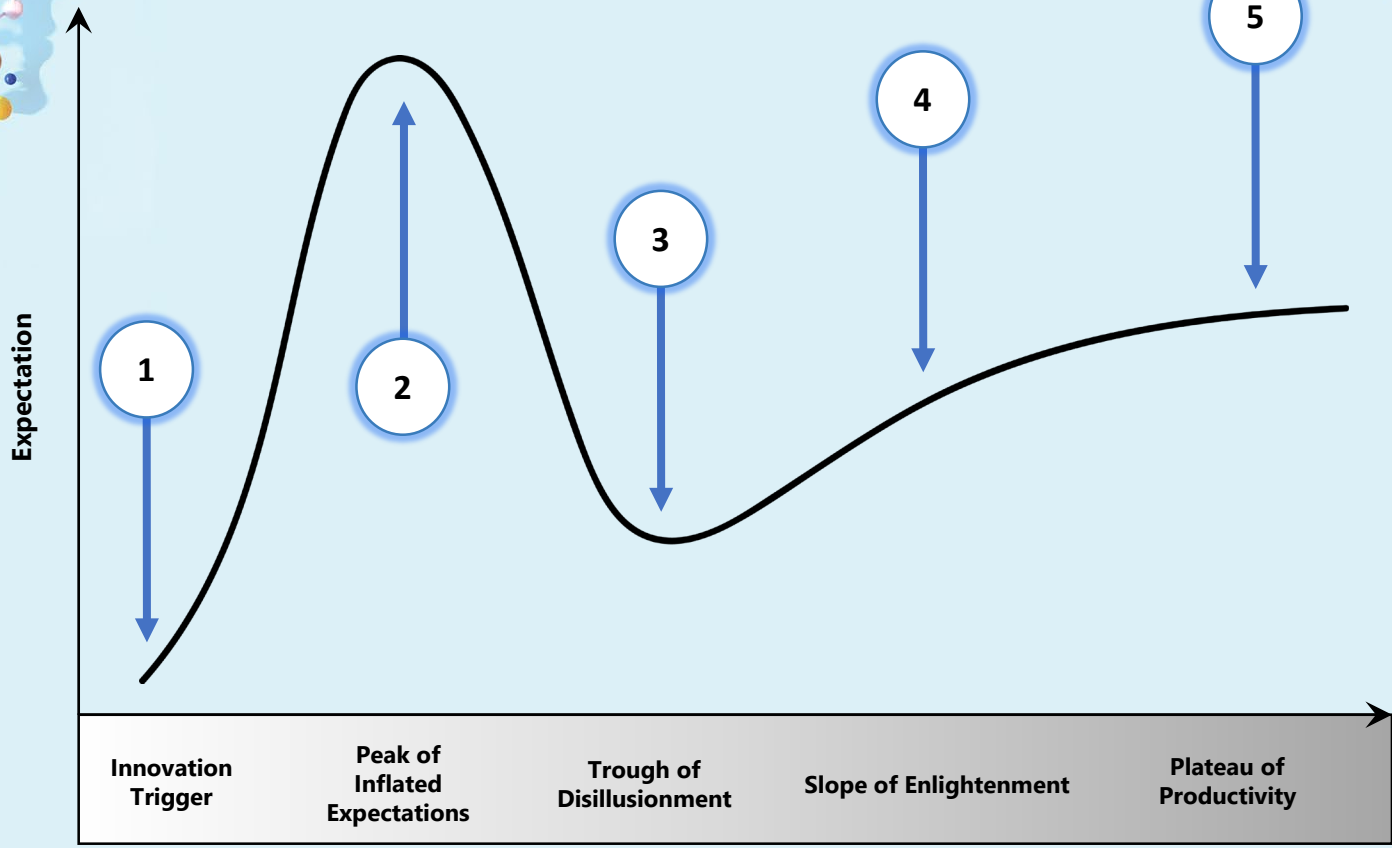


**Knowledge
Management and
Communication**



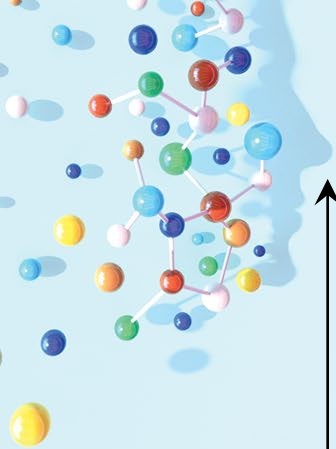
Regulatory Science Hope-Hype Cycle

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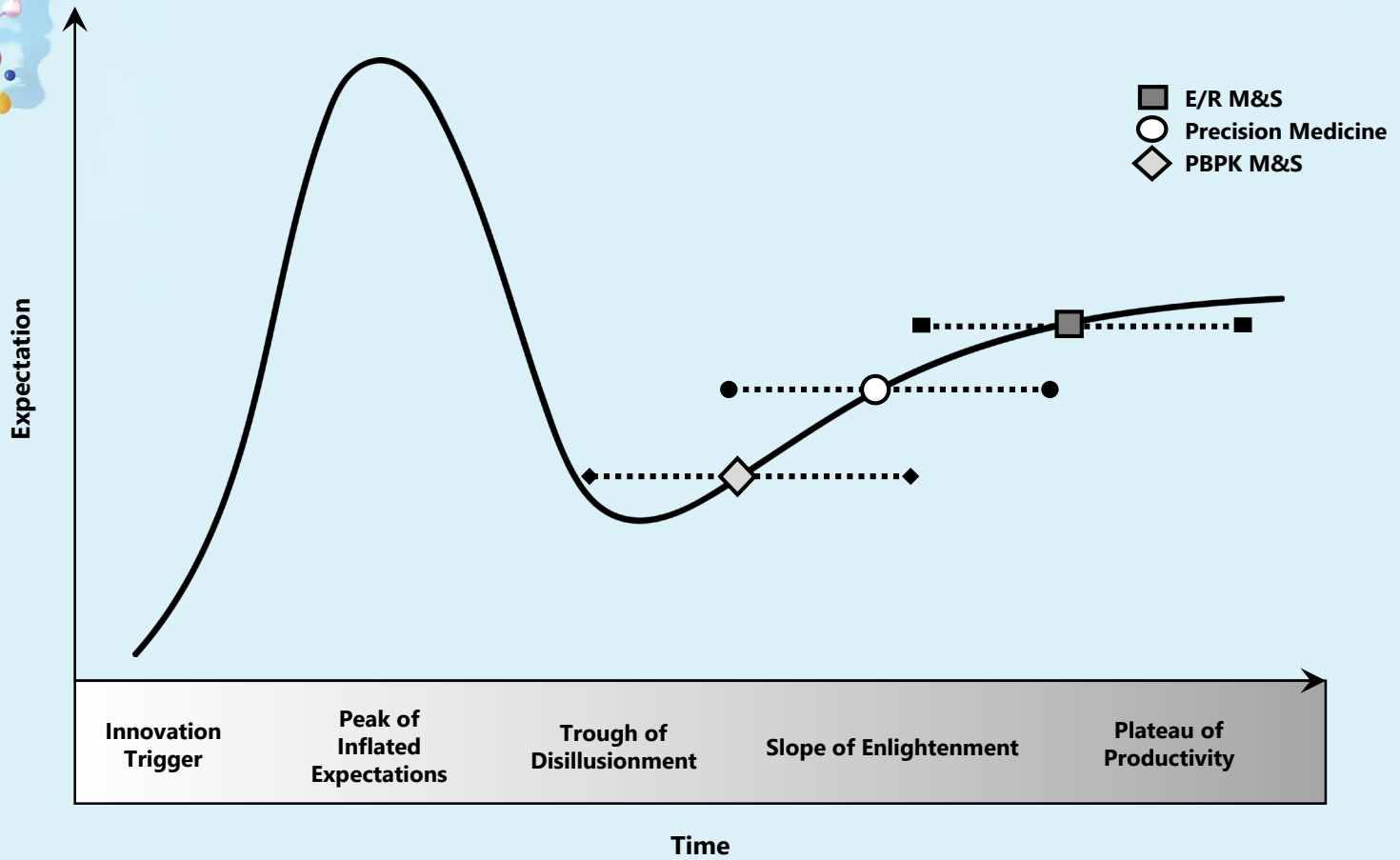
Modified from Gartner

Time

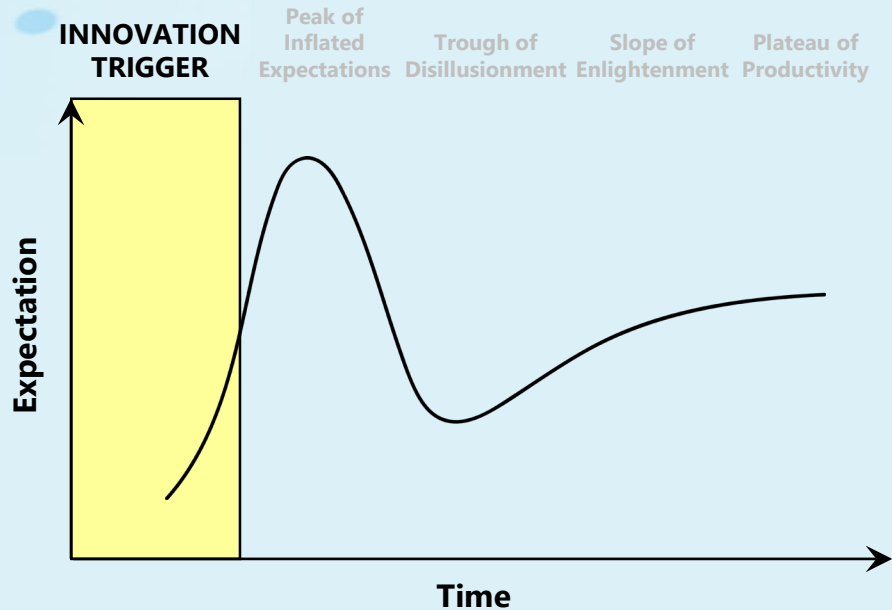


Regulatory Science Hope-Hype Cycle

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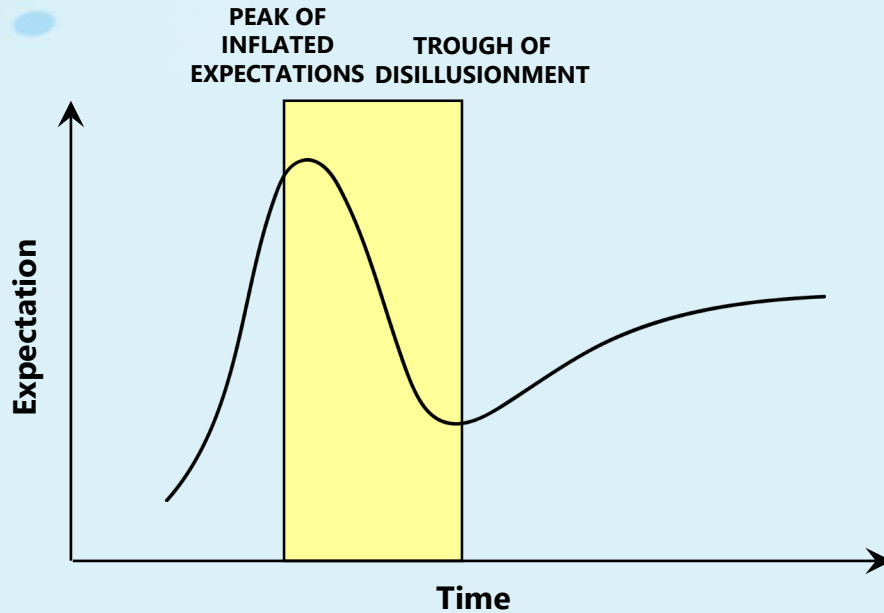


Exponential Growth and Enthusiasm Around Endless Possibilities



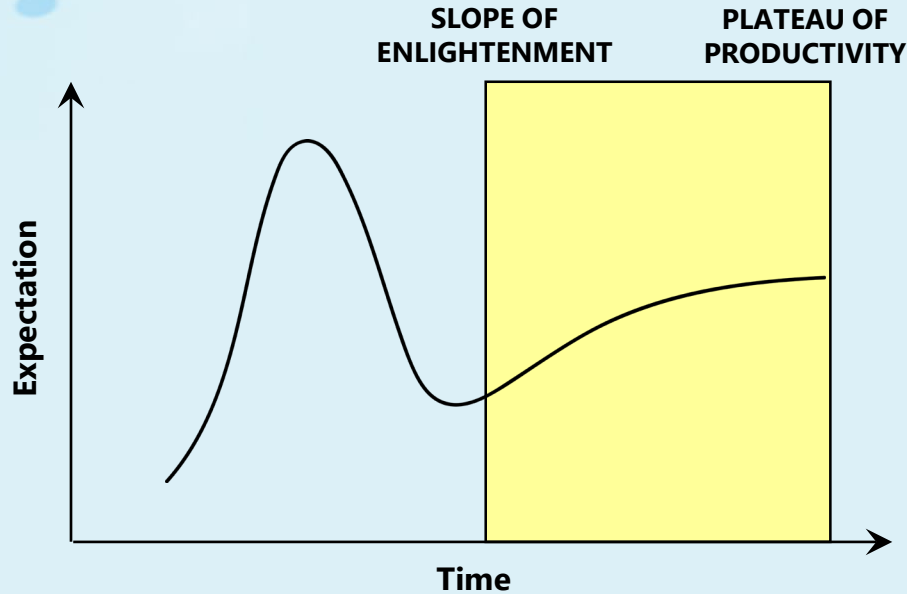
- Quantum leap in science or methodology
- Development of enabling tools and technology (e.g., software)
- Acknowledgment by senior leadership
- Significant public interest

Barriers to Translation – The Beginnings of Disillusionment and Recalibration



- Constraints of the science
- Steep learning curve
- Few instructional cases
- High organizational activation energy

A Second Convergence: Toward the Aspirational State



- Growing championship among decision- and policy-makers
- Public engagement
- Development of business process and workflows
- Development of best practices and regulatory guidances

Reflections on the Plateau of Productivity

- In the regulatory context, the scientific approach becomes more integrated and mainstream within the broader exercise of regulatory evaluation
- This aspirational state is the balance of expectations with realized benefit and risk
- Critical mass of experience needed to overcome residual skepticism from earlier eras of outsized promise
- Socialization (educational, experiential) a key component
- Context-specific caveats and perpetually more work to be done

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Is QSP on a Similar Path?

Systems Pharmacology: Bridging Systems Biology and Pharmacokinetics-Pharmacodynamics (PKPD) in Drug Discovery and Development

Piet H. van der Graaf • N

Preclinical QSP Modeling in the Pharmaceutical Industry: An IQ Consortium Survey Examining the Current Landscape

Marjoleen J.M.A. Nijssen^{1*}, F
Jerome T. Mettetal⁷, Patricia
Mark Penney¹⁴, Brian Topp¹

Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation

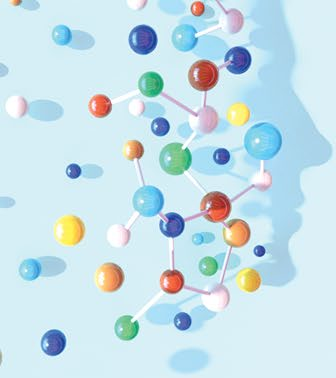
EFPIA MID3 Workgroup: SF Mar
B Hamrén⁷, L Harnisch¹, F Ivano
SAG Visser¹⁴

Best practices to maximise the use and re-use of QSP models Recommendations from the UK QSP Network

Lourdes Cucuru
Mark Penney, /
Paolo Vicini, Ja

A Survey of Software Tool Utilization and Capabilities for Quantitative Systems Pharmacology: What We Have and What We Need

Sergey Ermakov^{1*}, Brian J. Schmidt², Cynthia J. Musante³ and Craig J. Thalhauser²

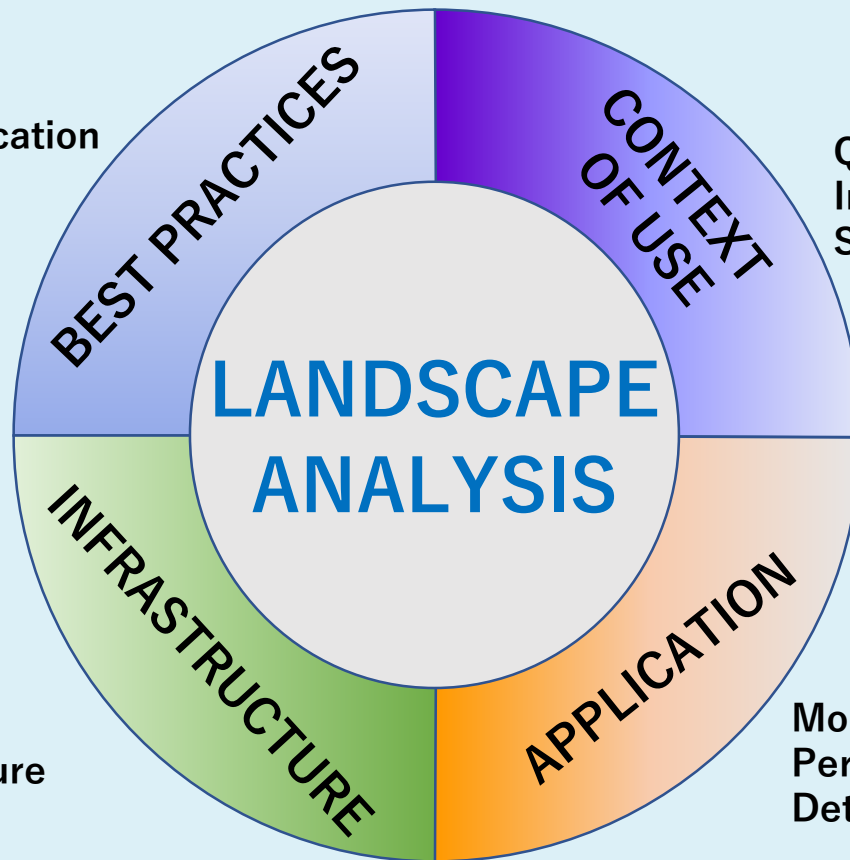


What is the QSP Community Doing Right? (1)

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- Frontloaded effort to identify specific applications of QSP that have the greatest value proposition
- Concerted effort to “contextualize the current status of QSP based on its multidisciplinary roots and its historical successes and challenges in order to establish its next direction” (Musante CJ CPT:PSP 2016)
- Landscape analysis and communication of current state (industry practices) → may mitigate the potential for overinflated expectations

Model Development
Model Vetting
Documentation
Reporting/Communication



QSP modeling definition
Intended use
Stage of model initiation

Resource investment
Organizational structure
Platform capabilities

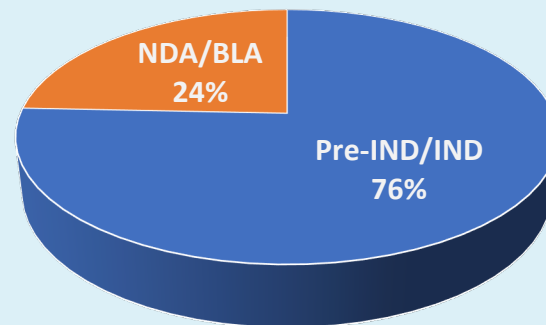
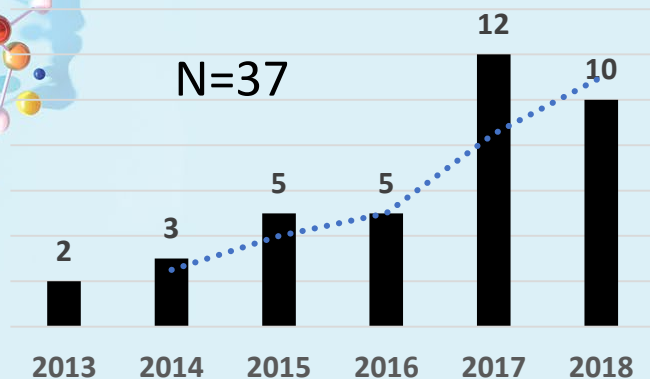
Model size and complexity
Perceived impact
Determinants of success/failure



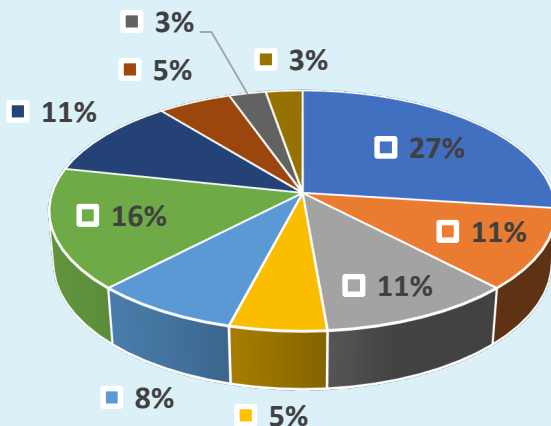
What is the QSP Community Doing Right? (2)

- The QSP community has taken a deliberative approach to address key questions facing the discipline
- The specific applications of QSP to drug development have been illustrated through case studies and landscaping
- Enabling technological capabilities have been articulated by end-users
- Best practices in communicating model context of use, development, validation/verification, and impact have been proposed
- Expectations appear to be appropriately set against which to benchmark gains afforded by QSP in drug development

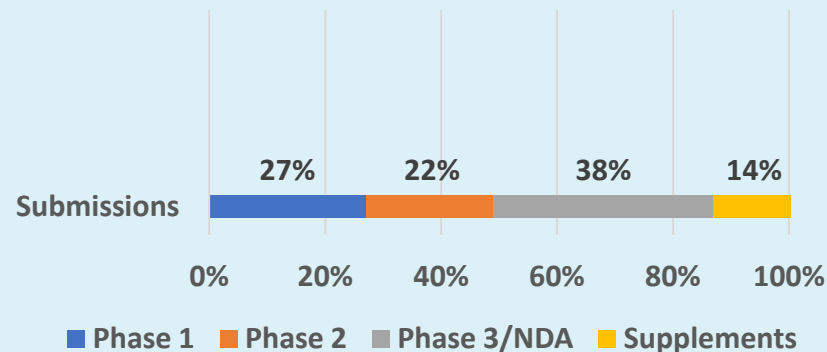
QSP in Submissions to the US FDA

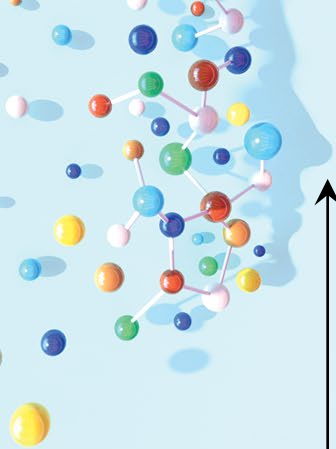


- Oncology
- IEM
- Hematology
- Neurology
- Metabolic/Endo
- Anti-infectives
- Cardiorenal
- Bone/Repro/Uro
- Rheum
- Pulmonary

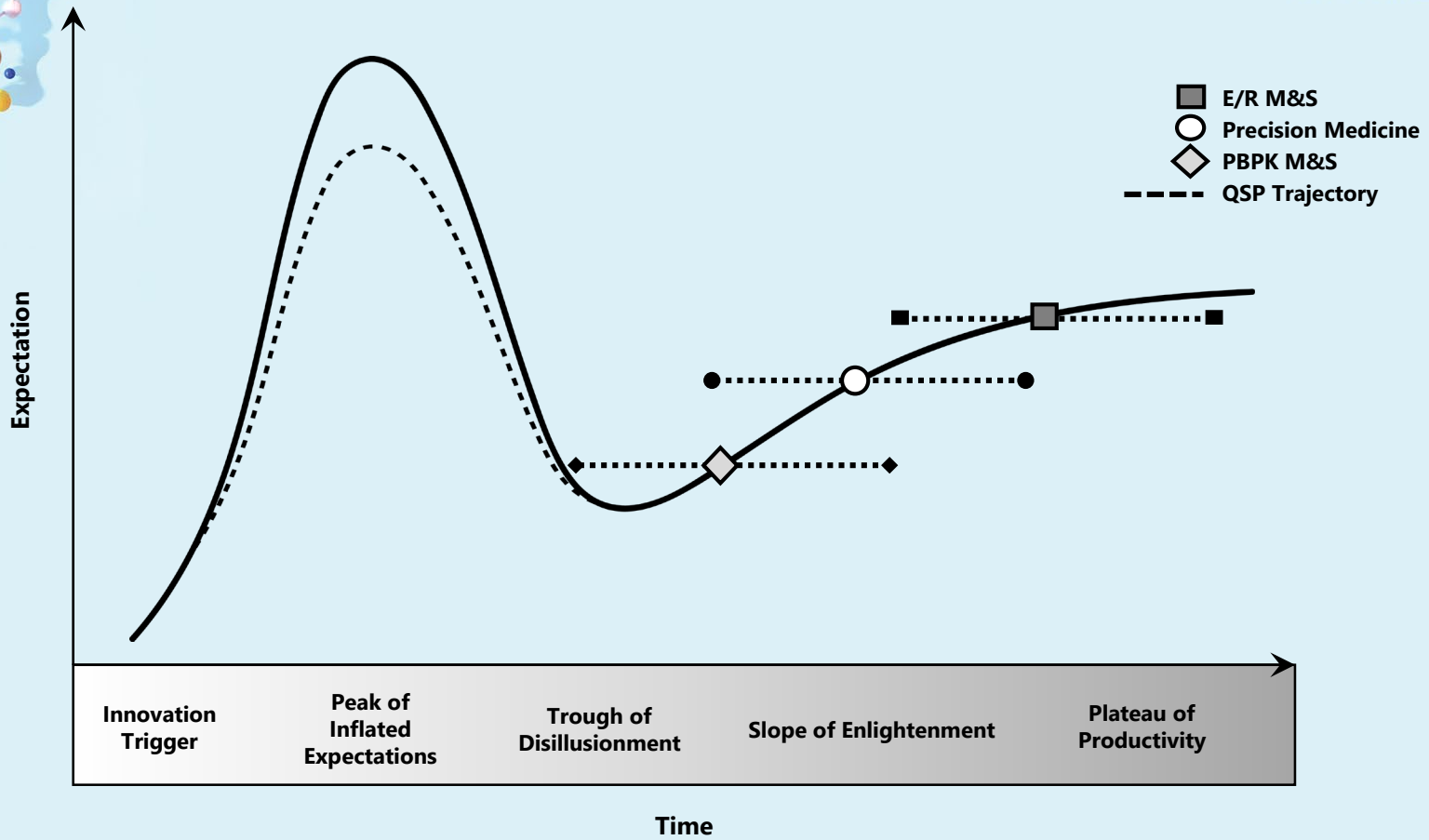


Stage in Development





The QSP Trajectory





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Outstanding Questions

- What is the role of regulatory scientists in evaluating QSP models and output in regulatory decision-making?
- What should the evidentiary framework and regulatory expectations be for model credibility assessment based on various use contexts?
- What is the appropriate time, mechanism, and purpose to engage with regulatory authorities on discussions about QSP in specific product development programs?

Issue-Based Approach to Engagement

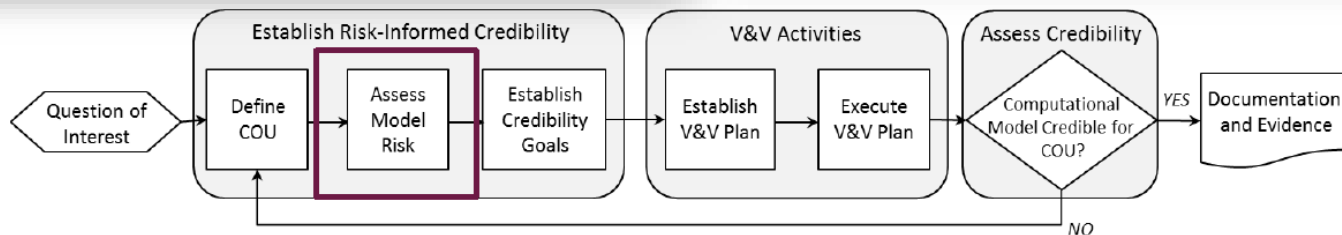
- What is the intended purpose and context for the given quantitative approach?
 - Is the modeling (with or without accompanying simulation) intended to be mechanistically explanatory of an observed phenomenon?
 - Is the exercise intended to be used for clinical trial planning?
 - Is the output intended to stand in for a clinical trial?
- Very different situations that would necessitate different conversations:
 - Some may not necessitate a conversation at all
 - Others would require dialogue around model credibility, decision risk, and resulting evidentiary requirements.

Risk-Informed Credibility Framework



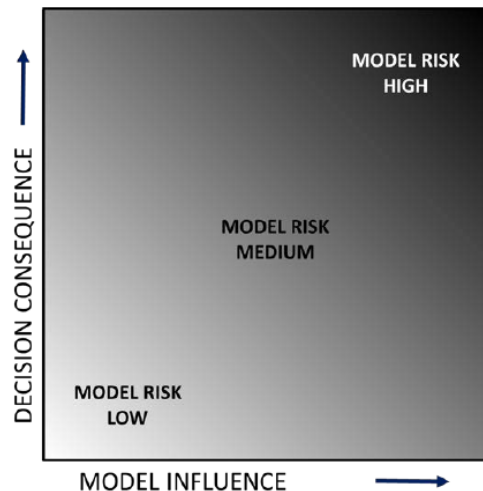
In order to more fully leverage computational modeling and simulations for medical products and clinical care, we need a methodology to ensure appropriate credibility.

Credibility: the trust, through the collection of evidence, in the predictive capability of a computational model for a context of use



Model risk is the possibility that the computational model leads to an incorrect decision that results in patient harm and/or other undesirable impacts.

- **Model influence** is the contribution of the computational model relative to other available evidence in making a decision.
- **Decision consequence** is the significance of an adverse outcome resulting from an incorrect decision.





Summary

- Many stakeholders are working to clearly define the QSP space
- There has been a concerted effort to share experience and communicate good practices
- Lessons can be learned from precedent regulatory sciences that may help proactively drive QSP through the Hope-Hype Cycle and perhaps to routine application
- As the science develops and more examples of QSP application reach the regulatory doorstep, further engagement among scientists involved in MIDD will be important

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