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, Zhihua Li, Rajnikanth Madabushi, Michael Pacanowski, and Yaning 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

1993-1997: PDUFA I - Review backlog
1998-2002: PDUFA II - Review times and procedures
2003-2007: PDUFA III - Increased interaction; support for post-market safety
2008-2012: PDUFA IV - Enhance pre-market review; modernize post-market safety system
2013-2017: PDUFA V - Review+ comms enhancement; strengthen regulatory science & post-market safety; electronic data standards
2018-2021: PDUFA VI - Program/process enhancement; HR; IT; enhance regulatory science & promote innovative tools

Modified from J. Barton, OSP/CDER/FDA
Opportunities for MIDD:
PDUFA VI – Enhancing Regulatory Decision Tools To Support Drug Development and Review
Regulatory Science Hope-Hype Cycle

1. Innovation Trigger
2. Peak of Inflated Expectations
3. Trough of Disillusionment
4. Slope of Enlightenment
5. Plateau of Productivity

Modified from Gartner
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
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
Is QSP on a Similar Path?
What is the QSP Community Doing Right? (1)

• 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
**LANDSCAPE ANALYSIS**

- **BEST PRACTICES**
  - Resource investment
  - Organizational structure
  - Platform capabilities

- **CONTEXT OF USE**
  - QSP modeling definition
  - Intended use
  - Stage of model initiation

- **APPLICATION**
  - Model size and complexity
  - Perceived impact
  - Determinants of success/failure

- **INFRASCTURE**

- **Model Development**
- **Model Vetting**
- **Documentation**
- **Reporting/Communication**
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

N=37

Submissions to the US FDA:
- **Pre-IND/IND**: 27% (76%)
- **NDA/BLA**: 24% (24%)

- 2013: 2
- 2014: 3
- 2015: 5
- 2016: 5
- 2017: 12
- 2018: 10

Stage in Development:
- **Phase 1**: 27%
- **Phase 2**: 22%
- **Phase 3/NDA**: 38%
- **Supplements**: 14%

Therapeutic Areas:
- **Oncology**: 11%
- **IEM**: 3%
- **Hematology**: 5%
- **Neurology**: 3%
- **Metabolic/Endo**: 38%
- **Anti-infectives**: 16%
- **Cardiorenal**: 11%
- **Bone/Repro/Uro**: 8%
- **Rheum**: 5%
- **Pulmonary**: 5%
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
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.
In order to more fully leverage computational modeling and simulations for medical products and clinical care, we need a methodology to ensure appropriate credibility.

**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.

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