PERSPECTIVE

# Perspective on model-informed drug development

**Model-informed drug development (MIDD) is a process intended to expedite drug development, enhance regulatory science, and produce benefits for patients. Quantitative modeling and simulation—principally by population pharmacokinetics (PK), exposure–response, and physiologically based pharmacokinetic (PBPK) analysis—is the technology that provides the capability to deploy MIDD across a range of applications. MIDD was codified in the 2017 Prescription Drug User Fee Act Reauthorization [1] (PDUFA VI, 2018–2022) and a performance goal was a MIDD pilot program to hold 2 to 4 industry–U.S. Food and Drug Administration (FDA) paired meetings quarterly through 2022.**

## DEFINITIONS

The following are other MIDD-related terms: model-based drug development (MBDD), model-informed drug discovery and development (MID3), drug discovery, development, regulation and utilization continuum (DDRU), quantitative pharmacology (QP), quantitative systems pharmacology (QSP), and integrated pharmacometrics and systems pharmacology (iPSP).[2-5] They convey the same underlying meaning. We need a common definition of MIDD that is understandable and consistently used. It will better support the application of quantitative methods to create value and make better decisions than having new terms every few years.

## EVOLUTION

MIDD is not brand new or innovative *per se*. Modeling and simulation (M&S) have been used by industry and regulators for the past 25 years. The International Conference on Harmonization (ICH) issued a "Dose-Response Information to Support Drug Registration Guideline (ICH E4, Database.ich.org/sites/default/files/E4_Guide line.pdf)" in 1994 that provided context for MIDD. This guideline recommended that studies be designed and conducted to assess the relationships among dose, drug blood concentrations, and clinical response throughout the development of a new drug using various statistical and pharmacometric techniques. Complementary guidance for industry from the FDA followed including "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" (1998, www.fda.gov/media/71655/download), "Population Pharmacokinetics" (1999, www.fda.gov/media/71364/download), "Exposure-Response Relationships" (2003, www.fda.gov/media/71277/download), and "PBPK Modeling" (2018, www.fda.gov/media/101469/download). Other guidelines have been issued by the European Medicines Agency and the Pharmaceuticals and Medical Device Agency in Japan to coordinate global activities related to MIDD.

The following two seminal publications presented ideas of great importance to MIDD: the "learn-confirm" paradigm described by Lewis Sheiner[6] and the interpretation of "confirmatory evidence" by Carl Peck et al.[7] as sanctioned by Sec. 115a of the FDA Modernization Act of 1997 (FDAMA).[1]

These guidance and publications formed a "canon" of knowledge that gave crucial identity to MIDD as a specific process and curriculum for education in the science of "quantitative pharmacology."

## CURRENT STATUS

MIDD is deployed by industry to assess and identify potential risks that may jeopardize the safety, efficacy, and financial prosperity of their assets. Regulatory reviewers assess the data from sponsors using a collection of quantitative techniques and value judgments to inform decision-making. Prior to PDUFA VI, MIDD principles were not routinely applied in the drug development process. It is not clear to what degree MIDD has improved the efficiency of drug development or addressed industry concerns about consistent and uniform acceptance of MIDD within the FDA review divisions. Negotiations leading up to PDUFA

VII (2023–2027) are underway, and the results will influence the future of MIDD. This would be a perfect time for the FDA to consolidate PDUVA VI experiences with MIDD and share them publicly and for industry and the FDA to articulate their experiences with the MIDD paired meeting pilot program and other interactions during Investigational new Drug (IND) application meetings and New drug application or new biologic license application (NDA/BLA) reviews. Convening future public workshops and clinical pharmacology advisory committee meetings to focus on the overall status of MIDD and future plans for a MIDD draft guidance would help reassure the industry of the sustainability of this activity.

## INDUSTRY ADOPTION

Drug development is far more complex than ever. MIDD can fuel both enthusiasm and apprehension among pharmaceutical companies. In my experience as an industry consultant, I have seen a wide gap among organizations in the extent to which they apply the process of MIDD. Some may focus on a single task of dose selection using empirical modeling of PK and pharmacodynamics in early drug development. Others may use quantitative analysis for decision-making across the lifecycle stages of drug development from target identification to postmarketing commitments.

What can be learned from this dichotomy to improve our understanding of the MIDD adoption process in industry? I do not have valid answers. The factors are too complex to generalize. Culture is important: how MIDD is perceived by leadership to have incremental advantages over alternatives and the degree to which MIDD is compatible with existing drug development practices. Organizational structure is important: Are functional specialties such as pharmacometrics and biostatistics aligned or is there competition for influence, budgets, and resources? Execution is important: Is modeling and simulation seen as too time-consuming and difficult to deploy given the expertise and experience of scientists and pending submission deadlines? Reception is important: positive regulatory outcomes during IND meetings and from NDA/BLA reviews when using MIDD will motivate continued use by industry, whereas negative experiences with dissuade further investment.

## REGULATORY ADOPTION

Advancing MIDD is a commitment of PDUFA VI. The FDA has convened workshops, published scientific papers, and launched the paired meeting pilot program. However, routine adoption of MIDD principles within the review stream of INDs and NDA/BLAs within the FDA is far more complex because of the heterogeneity and diversity of opinion across the therapeutic areas. What industry would like to know is to what degree has MIDD has been institutionalized and been receiving the attention and support of upper management across the therapeutic areas? One of the frequent questions that I receive in consulting is "Will FDA accept my data analysis, model and position, and what are the risks if they don't?" Getting answers to these questions are difficult without more transparency. It is beneficial to look into the public domain and the executive summaries of NDA/BLA multidisciplinary reviews and evaluations published at drugs@FDA. The clinical pharmacology review and pharmacometrics appendixes will provide additional insight into the influence that M&S activities have had on recommendations, labeling and top-level medical officer conclusions about the substantial evidence of effectiveness, and the benefit–risk summary and assessment of the drug.

## QSP

The newest and most sophisticated component of MIDD is QSP modeling, used alone or in combination with other model-based tasks such as PBPK-QSP. QSP models have merits and shortcomings and at this time are of more value to industry than regulators. Some have lamented that the time and costs of collecting, modeling, and interpreting data from QSP modeling exceed its benefits, particularly when there are simpler models to answer the question. Engineers and technologists have referred to QSP as a technology push strategy in which research and development creates market interest in a range of new products based on innovative solutions to customer problems. In contrast, PBPK represents a market–pull approach designed to provide improvements to existing products that the market or potential customers demand as solutions to their problems. This distinction makes a difference because technology push strategies carry a lower risk of acceptance by regulatory agencies due to limited experience and have a monumental need to justify the additional complexity and cost of data acquisition to upper management. We have seen QSP models deliver on some long-delayed promises in MIDD such as identifying previously "undruggable targets" and optimizing combination therapy in cancer. For example, sotorasib, which targets *KRAS G12C* mutations in lung cancer, represents a successful application of QSP modeling during the early drug development process.[8] But QSP for regulatory decision-making comes with a daunting set of challenges and uncertainties, and there has been a scarcity of successful examples. Despite this, an increasing number of QSP submissions has been reported to have been submitted to the FDA during the past 5 years although it is not clear how they were used in NDA/BLA decisions.[9]

Of course, things can change overnight if several "fit for purpose" QSP models present themselves to the FDA as a better approach to early dose selection and late-phase dose optimization, an improved strategy to better understand pharmacodynamics, how to select patients for clinical trial enrichment, or to otherwise support labeling claims. As one example, we have seen how the FDA's approval of aducanumab for treating Alzheimer's disease has set in motion a significant ripple effect that appears to have redefined the regulatory standard for accelerated approval and the use of reduction in amyloid beta plaques in the brain as a new surrogate end point for clinical decline in dementia. The recent launching by the FDA of the "Drug Development Tools: Fit-for-Purpose" initiative may provide a future pathway for qualification of QSP models for regulatory use.

## FINAL THOUGHTS

The current technology of MIDD—population PK, exposure–response, and PBPK modeling and simulation—is at a plateau in terms of what is available right now for day-to-day use. As they say, "the easy stuff is done." A technology plateau is not a bad thing. MIDD is inherently computationally intensive, and this necessitates a significant ramp-up of education and training of additional scientists in modeling and simulation proficiency through academic online certificate programs and formal resident research programs in applied pharmacometrics to sustain the growth in MIDD.

One could also argue that MIDD has not reached its apex and has only begun to deliver on the promise of expediting and improving the success of drug development, enhance regulatory decision-making, and produce clinical benefits for patients. The stage is set for a new plateau when we can marry classical pharmacometrics and systems pharmacology with "hot topics" such as real-world data, pharmacoepidemiology, and artificial intelligence with its subsets of machine learning and neural networks.[10] Another area of untapped potential is precision dosing. The FDA sponsored a workshop recently to define the need for model-based approaches to deliver individualized drug dosing to the bedside in the real-world setting. Innovations such as these can provide a "jolt" to MIDD and move the technology to a new plateau. That would be "good money" for MIDD.

Last but not least, recognize that MIDD is a "team sport." One cannot emphasize enough the importance of communicating the results of often complex modeling and simulation exercises to decision-makers and upper management in industry or to multidiscipline review teams in the FDA.[11] Pharmacometricians need to be ready to step up, express opinions, and make recommendations based on their modeling and simulation efforts. Let's keep the momentum going!

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