Reflections on model-informed drug development

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Model-informed drug development (MIDD) and its complementary initiative, the MIDD Paired Meeting Pilot Program (MIDD Pilot), have become an appropriate catchphrase for the strategic approach of using computational models and simulations to inform critical drug development and regulatory decision making (**Figure 1**).

The early development of MIDD began piecemeal nearly 27 years ago when the US Food and Drug Administration (FDA) Modernization Act (FDAMA) of 1997 was signed into law. It amended the Federal Food, Drug, and Cosmetic (FD&C) Act and modified the mission of the FDA to include a goal of accelerating research, catalyzing innovation, and increasing access to care.[1] Certain provisions of the Act gave the FDA greater flexibility in drug approval and influenced the rapid growth of incorporating computational models in drug development. Among the numerous provisions of the Act, Section 115a was noteworthy. It allowed the determination of substantial evidence of effectiveness as required for approval of a new drug to be based on data from one adequate and well-controlled clinical trial and confirmatory evidence.[2] In order to understand FDA's application of the confirmatory evidence standard, the Agency issued the 1998 guidance for the industry on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.[3] In this guidance, the FDA anticipated that confirmatory evidence would arise from mechanistic or pharmacodynamic data, correlations between systemic drug exposure and clinical response, and well-defined pharmacokinetic-pharmacodynamic (PKPD) relationships. It followed that robust standards of modeling and simulation would facilitate demonstration of a drug's efficacy and safety. A pivotal milestone in the evolution of MIDD was the FDA guidance on exposure–response relationships that was issued in 2003. It provided specific direction to sponsors by laying out a structured approach to study design, model-based data analysis, and regulatory applications.[4]

In 2004 the FDA launched the Critical Path Initiative (CPI), which offered a choice between innovation or stagnation in drug development.[5] The CPI was intended to address the gap between scientific discoveries and the delivery of new, innovative medical products. A critical part of the CPI was to promote the concept of model-based drug development (MBDD), in which pharmaco-statistical models of drug efficacy and safety should be developed across the drug development continuum from preclinical through to clinical phases. MBDD included refinement of quantitative clinical trial modeling using simulation software to improve dose selection, trial design, and prediction of outcomes. A crucial aspect of MBDD which the CPI emphasized was improving drug development knowledge and regulatory decision making.

Paired meetings between the FDA and industry played a crucial role in facilitating interactions between regulatory scientists and pharmaceutical sponsors of investigational new drug (IND) applications and advancing the principles of MIDD. Under a pilot program started in 2004, the FDA conducted a series of end-of-phase 2A (EOP2A) meetings with the

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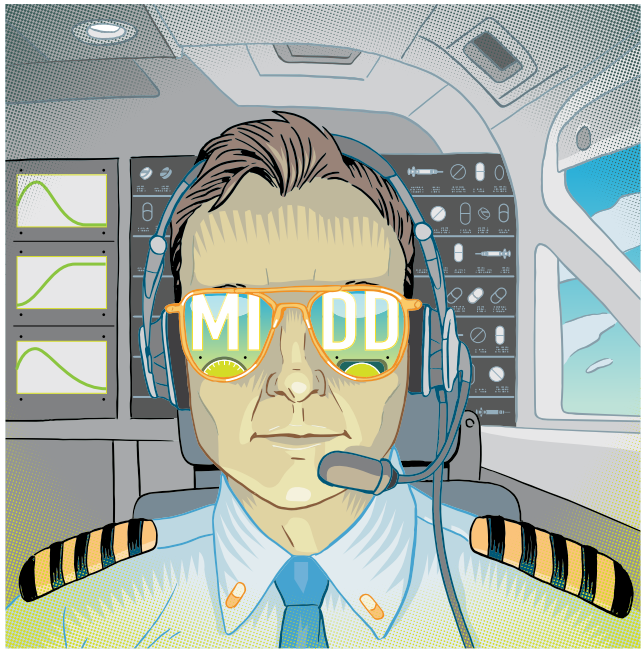

Figure 1 *Clinical Pharmacology & Therapeutics* August 2024 cover image: "Reflections on MIDD."

primary focus being the use of modeling and simulation to inform the design parameters of subsequent pivotal trials and dosage regimen choices. Based on the positive experiences of the pilot program for both regulatory authorities and pharmaceutical sponsors, in 2009, the FDA proactively issued the EOP2A Meeting Guidance which offered an opportunity for dialogue on the important aspects of modeling and simulation for the purpose of transitioning from exposure–response relationships derived from early phase clinical trials to selecting optimal dosing regimens for the pivotal phase IIB and phase III clinical trials.[6] Topics for discussion included horizontal integration of preclinical–clinical exposure–response models, clinical validation of biomarkers, and implications of pharmacogenetics on PK, PD, or both.

MIDD received formal recognition from industry and the FDA, and was established as part of the Prescription Drug User Fee Act (PDUFA) VI of 2017.[7] There was a stipulated commitment to enhance regulatory science and expedite drug development using physiologically-based pharmacokinetic (PBPK), exposure–response and disease progression models and simulations (collectively referred to as MIDD). PDUFA VI also enabled the launch of the MIDD Pilot Program in 2018, with stated goals that were not unlike those in the EOP2A meeting guidance. Subsequently, based on the shared experiences and consensus on the successful impact of MIDD and the paired meeting pilot program, the PDUFA VII (2023–2027) provisions committed the FDA to a continuation and expansion of MIDD.[8] While MIDD is still evolving into a distinct regulatory pathway—such as traditional new drug/biologics license application (NDA/BLA) processes—MIDD paired meetings are not yet considered a milestone meeting (e.g., Type A or Type B meeting) between the FDA and sponsors, as is delineated in PDUFA VII and in a recent FDA meeting guidance.[9] However, MIDD approaches significantly enrich discussions between regulatory scientists and pharmaceutical sponsors by providing a rigorous and scientifically grounded framework that focuses on a shared understanding of optimal dosing and pivotal clinical trial designs, as well as identifying potential issues that may impede NDA/BLA submissions and market approval.

In the current issue of *Clinical Pharmacology & Therapeutics* (*CPT*), Madabushi and coworkers from the FDA provide an overview of their experience with the paired meeting Pilot Program, which ran from 2018 to 2022.[10] In this period, a total of 63 meeting requests were received, of which 50 (~80%) were selected. The vast majority (~85%) of the submissions were related to late stage (phase II and III) or post-approval development. There was an even split between small molecule and biological therapeutics, and oncology and neurology were the main therapeutic areas. More than

half of the submissions involved application of conventional MIDD analyses, such as dose/exposure response and population PK; however, almost one-third used mechanistic approaches, such as semi-mechanistic PKPD, PBPK, and quantitative systems pharmacology (QSP). An example of the impact of the Pilot Program is the fact that it was directly responsible for the regulatory approval of new patient-centered dosing options for 4 previously approved drugs (sotalol, ramicirumab, cetuximab, and valbenzanine), with MIDD approaches alleviating the need for additional clinical trials.[10] A recent example reported in this issue of *CPT* is the concept of model-informed "pharmacodynamic bioequivalence," which supported the switch to a novel controlled-release formulation of an antidepressant in late-stage development.[11] An industry perspective on the benefits realized from Pilot Program was presented in a previous issue of this journal.[12]

From an FDA point of view, the key elements to success include obtaining leadership engagement and buy-in, education,[13] process flexibility, and transparent communication.[10] The ingredients to optimize the value of the MIDD Program from an industry perspective are reviewed in a White Paper in the current issue from the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ), which can serve as a guide for sponsors for future meetings.[14]

The FDA has demonstrated its commitment to innovation in drug development for over a generation. MIDD and the paired meeting program stand out as major innovations in regulatory science that leverages advanced modeling and simulation technology to make better regulatory decisions. In addition to benefiting the industry, MIDD directly impacts patients by enabling higher quality NDAs/BLAs and approved drug labels with more meaningful information for healthcare providers to apply to their patients.

Looking ahead, the FDA has signaled its commitment to further innovations in MIDD aimed at advancing QSP models through participation in workshops and conferences, as well as publications on trends in QSP submissions in NDAs/BLAs[15] and the recent establishment of the Center for Drug Evaluation and Research (CDER) Quantitative Medicine (QM) Center of Excellence (CoE).[16] Exactly how much MIDD will succeed in improving the probability of drugs progressing from first dose in man to market approval, compared with historical norms, will be closely monitored over the next 5 years.

Lastly, the FDA has not neglected its responsibility to other major international regulatory partners and industry members through its participation in the International Council for Harmonization (ICH).[17] The new overarching ICH M15 MIDD General Principles Guideline will aim to facilitate greater and wider adoption of MIDD principles in drug development and regulatory decision-making across the major ICH regions (Europe, Japan, and the United States), and among the standing worldwide regulatory and industry members, as well as ICH observers (e.g., the World Health Organization).

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CONFLICT OF INTEREST

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