

Industrial Perspective on the Benefits Realized From the FDA's Model-Informed Drug Development Paired Meeting Pilot Program

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The US Food and Drug Administration (FDA) Model-Informed Drug Development (MIDD) Paired Meeting Pilot Program was created to facilitate the application of MIDD principles¹ to drug development. Industry has actively participated in this opportunity, and the quantitative and qualitative benefits of participation are discussed in this report.

THE FDA MIDD PAIRED MEETING PILOT PROGRAM

The main goals of the program are to: (i) Provide an opportunity for drug developers and the FDA to discuss the application of MIDD approaches to the development and

regulatory evaluation of medical products, and (ii) provide advice about how particular MIDD approaches can be used in a specific drug development program.² During Prescription Drug User Fee Amendments VI (PDUFA VI) negotiations, both the FDA

and industry scientists discussed the need to enhance application of MIDD approaches in drug development programs.³ Thus PDUFA VI established the FDA MIDD Paired Meeting Pilot Program, which was initiated in 2018 as a program jointly administered by the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. The paired meeting program provides an opportunity for drug developers and the FDA to iteratively discuss how proposed MIDD approaches can be used in a specific drug development program. Since its inception through the first quarter of 2021, the FDA has received 34 meeting requests and granted 30 of the requests. There have been projects at every stage of development, from preclinical to postapproval, and they span a large number of therapeutic areas.⁴

To obtain a current industry perspective on the value of the program, a recent survey of participating companies was conducted by the International Consortium for Innovation and Quality in Pharmaceutical Development of its member companies. The focus of this survey was to assess potential benefits of the program as an aid in the consideration of the program's continuation. Results of the survey are summarized below.

INDUSTRIAL PERSPECTIVE OF THE MIDD PAIRED MEETING PROGRAM BENEFITS

Each of the survey respondents provided a list of characteristics and declared benefits

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for programs associated with the paired meeting pilot program. The 19 examples collected represent approximately two-thirds of the pilot program cases to date. Similar to characteristics of all cases,³ the examples in this paper cover the range of development stages, a variety of therapeutic areas, and the primary topics addressed at the MIDD meetings (**Figure 1**). Inspection of the reported benefits found that they could be categorized into three broad categories: efficiency, alignment, and learning and clarity.

MIDD principles have been touted as a mechanism for improving the efficiency of drug development,² which can be quantified as savings in both development time and cost. The examples from the survey, summarized in **Table 1** note significant estimated savings in time, up to 2 years for some programs. Additionally, there were substantial savings in resources, up to \$30–70 million in development costs. (Note, in cases where the benefits were quantified, time and/or development cost savings were calculated by contrasting a model-informed strategy with traditional development programs or pathways that would likely have been pursued without the MIDD pilot program interactions. Furthermore, time and cost savings

for each program were estimated assuming the program would advance to new drug application (NDA) submission.)

The estimated savings not only serve the pharmaceutical companies, they also provide significant value to patients and the medical community as successful medications will reach the market faster. Additionally, the savings on resources and cost of development can be applied to the advancement of additional promising candidates, and compounds that do not have acceptable safety and efficacy based on MIDD principles can be terminated or risks identified more efficiently with fewer patients or volunteers exposed.

Alignment was the second most cited benefit, and this was further subdivided into two types, alignment with the agency and internal alignment (**Table 1**). With respect to alignment with the FDA, companies noted that by focusing on a specific topic during the paired meetings, they were able to reach agreement on a development strategy. This is in contrast with other types of regulatory meetings, for example the end-phase-II meeting, as these are limited to a single meeting and typically cover a multitude of topics with little or no time

devoted to MIDD principles. The other alignment type is one that is not obvious, namely internal alignment. Applications of MIDD are not yet routine within and across all companies. Instances have been noted of MIDD strategies not being proposed because of uncertainty surrounding regulatory outcomes, and the time or preparation for implementation are considered too high or risky to explore the pathway, resulting in traditionally longer or more expensive development pathways. Previously, MIDD applications have been sporadic and largely opportunistic; opportunities for in-depth engagement between industrial and the FDA scientists have been limited.²

The MIDD pilot program offers a venue to overcome these limitations by filling the “communication gap” between modeling scientists and other disciplines and decision makers both within industry and between industry and regulators.⁵ The relatively small briefing package submitted with the initial request and the rapid response and review process² are considered a low hurdle for companies, which allows them to explore MIDD applications when they otherwise would not. The paired meeting format also allows for an extension of the MIDD

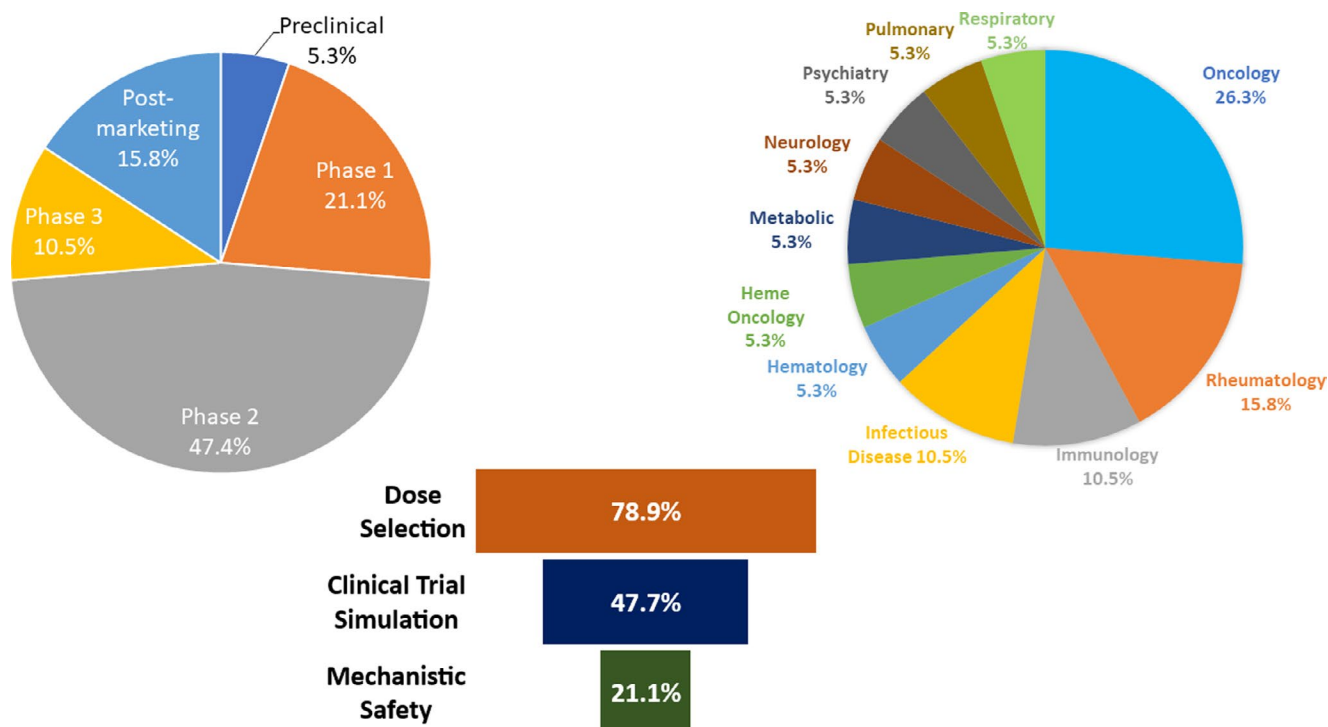


Figure 1 Characterization of programs considered in the Model-Informed Drug Development Paired-Meeting Pilot Program. The left chart depicts the phase of clinical development. The center chart depicts the discussion topics (a program could discuss more than one topic). The right chart depicts therapeutic areas and percentage of programs in that area.

strategy. When a favorable resolution for the primary MIDD aspect is met after the initial meeting, the FDA has encouraged use of the follow-up meeting for discussion of other applications of MIDD, which has been highly beneficial and appreciated. Further, as companies gain positive experiences with MIDD approaches, they are more inclined to consider future applications.

Table 1 Survey results: Industrial benefits from participation in the MIDD Paired-Meeting Pilot Program

Benefit	Response (number of responses)	Other responses
Time savings	<ul style="list-style-type: none"> • 0–3 months (2) • 3–6 months (0) • 6–9 months (0) • 9–12 months (2) • 12–15 months (1) • 15–18 months (1) • 18–24 months (3) • >2 years (3) • Other (7) 	<ul style="list-style-type: none"> • 3–6 months potential time savings but not realized as internal strategy changed • Too soon to provide estimation, but will be ≥ 12 months • Too soon to provide estimation, but will be ≥ 6 months • Too soon to provide estimation (2) • New pathway for a new avenue for approval that otherwise would not be pursued (infinite time savings) • Approximately 2 years
Mechanism for time savings	<ul style="list-style-type: none"> • Accelerated timelines to reach a go/no-go decision supported by simulated outcomes (6) • Obviating the need for a clinical trial in favor of a simulated outcome (e.g., PBPK extrapolation from adults to pediatrics) (6) • Reduced group sizes leading to faster trial recruitment and completion (3) • Obtaining approval based on a single pivotal trial plus totality of evidence supported by modeling and simulation (3) • Other (6) • Note: more than one mechanism could be submitted 	<ul style="list-style-type: none"> • No time savings were achieved yet, but the expected saving should mainly come from the accelerated timelines to reach a go/no-go decision supported by simulated outcomes • Obtained early feedback on feasibility of MIDD development path • Pathway for approval of an indication that otherwise would not be explored • Saved 2 months' time with respect to alternative regulatory interaction • Not applicable (2)
Developmental cost savings	<ul style="list-style-type: none"> • 0–1 million USD (1) • 1–10 million USD (2) • 10–30 million USD (2) • 30–70 million USD (3) • Not applicable (11) 	<ul style="list-style-type: none"> • Free text response for this item was not allowed in the survey
Mechanism of cost savings	<ul style="list-style-type: none"> • Smaller (reduced) trials (4) • Simulated outcomes replacing the need for clinical trials (e.g., PBPK in place of drug-drug interactions, reduced organ impairment studies) (4) • Did not use resources to test the wrong dose levels; getting to the right dose faster (4) • Evaluating PK/PD on less costly but validated biomarkers to demonstrate proof of efficacy and choosing the best doses to test in subsequent trials (2) • Other (6) • Not applicable (5) 	<ul style="list-style-type: none"> • Assumes successful trial • It is too soon to know the cost saving but they are expected to come mainly from not using resources to test the wrong dose levels—getting to the right dose, faster • Note although cost savings were not achieved, it allowed for a path to potential new indications • There may be some savings on material, even without running a trial • It is hard to translate the time savings into dollar amount, the decision is priceless but hard to quantify • Waiver of additional clinical trials would be the reason if the cost saving were achieved
Alignment	<ul style="list-style-type: none"> • Alignment between company and FDA <ul style="list-style-type: none"> ◦ 17 examples cited • Alignment among various groups within the company <ul style="list-style-type: none"> ◦ 16 examples cited 	<ul style="list-style-type: none"> • Selected responses: • Alignment with the FDA was achieved on: study design, intended disease, and population • Agreement on model-based dose selection to take into pivotal phase III study a dose not previously studied • Obtained clear feedback on the technical feasibility of the approach, and gained an appreciation of the broader issues that needed alignment within the FDA. Some line functions within the sponsor were skeptical with the novel approach • The alignment with the FDA gained significant traction and acceptability of the proposal • FDA therapeutic area representatives and key IRT members participated in the meeting (along with OCP M&S experts) provided internal sponsor confidence in the MIDD Pilot Program outcome • Well received internally; led to use by other teams • See Supplementary Materials for further details

(Continued)

Table 1 (Continued)

Benefit	Response (number of responses)	Other responses
Learning and clarity	• 17 examples cited	<ul style="list-style-type: none"> • The FDA provided valuable feedback to clarify their position on additional data that would be needed for further development and eventual approval of the treatment • Clear insight into the agency's technical expectations for MIDD and approach to decision making • Technical discussion with respective agency SMEs (Statistics, Clinical Pharmacology, and Pharmacometrics) was unprecedented • Getting informed and highly engaged external scrutiny of proposed MIDD strategy via the MIDD pilot mechanism gains confidence in implementing the approach • Became aware of the role of drug-excipient complexation on the interpretation of CYP3A DDI See Supplementary Materials for further details

DDI, drug-drug interaction; FDA, US Food and Drug Administration; IRT, interdisciplinary review team; MIDD, Model-Informed Drug Development; OCP M&S, US Food and Drug Administration Office of Clinical Pharmacology modeling and simulation; PBPK, physiologically-based pharmacokinetic; PK/PD, pharmacokinetic/pharmacodynamic; SME, subject matter expert.

Learning and clarity were also cited as significant outcomes of the pilot program discussions. Companies appreciated the insight that the FDA colleagues provided, including rationale for different preferred strategies, feedback on methodologies, additional data needed, and other requirements for eventual approval. With some projects, these clarifications have been pertinent to other programs at the sponsor companies that were applying similar development strategies. It was also noted that these interactions influence more than a single program as they serve to build consensus in the pharmaceutical industry, and they may provide early scientific interaction that helps shape future regulatory policy. Finally, companies have appreciated the opportunity to brainstorm with the agency about possible solutions through interactions with the wide variety of FDA subject matter experts that participate in these meetings. This collaboration between industry and the agency facilitates achievement of optimizing the development of new medicines for patients.

Eleven of the 19 programs have taken advantage of the paired meeting format, with several follow-up meetings still pending. The follow-up meetings ranged from 2 to 9 months after the initial meeting (median 3). Of those who have already participated in the second meeting, all followed up on discussions that were part of the initial meeting. Additionally, there were two cases in which the sponsor addressed new topics about the program and one case in which a topic that

was not part of the original program was discussed. These examples demonstrate how the MIDD initiative provides opportunities to expand the MIDD deliberations to other areas within or across development programs.

The experience of the participating companies with the FDA MIDD paired meeting program has been strongly favorable. The companies have recognized savings in resources, achieved alignment with the FDA on developmental strategies, and gained clarity on important aspects of programs and product characteristics. Further, these meetings have helped champion the application of MIDD strategies within pharmaceutical companies and have facilitated adoption of MIDD strategies across programs within a company. This initiative enhances the quality of conversation between the pharmaceutical company and the FDA by allowing a greater depth of discussion on key product characteristics and drug development strategy. The totality of evidence on the value of this program demonstrates a definite benefit to patients, the medical community, and pharmaceutical companies. Hence, the permanent adoption and expansion of these meetings and their principles is strongly encouraged.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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