Impact of Model-Informed Drug Development on Drug Development Cycle Times and Clinical Trial Cost

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Model-informed drug development (MIDD) integrates data to quantify benefit/risk informing objective drug discovery and development decisions. An additional critical benefit of MIDD is postulated to be improvement in trial and program efficiencies. While the application of MIDD has grown, there have been no clear examples across programs to demonstrate its value at the portfolio level. This manuscript offers a methodology and examples to demonstrate MIDD value in terms of time and cost savings. We utilized an algorithm to estimate savings based on MIDD-related activities at each stage of development across the entire drug development portfolio during a typical year between 2021 and 2023. This algorithm, although company-specific, demonstrated general applicability across several programs of the portfolio. Overall, the use of MIDD yielded annualized average savings of approximately 10 months of cycle time and $5 million per program. Systematic application of MIDD approaches yielded significant time and cost savings across the drug development portfolio in addition to informing data-driven decisions. Increased utilization of MIDD approaches is a driver for improving drug development efficiency.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Model-informed drug development (MIDD) integrates data to quantify benefit/risk, informing objective drug discovery and development decisions. The evolution of MIDD and its application to streamline the overall drug discovery, development, and regulatory evaluation processes is well-documented.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ While the application of MIDD has grown, there have been no clear examples across programs to demonstrate its value in terms of resource savings at the portfolio level.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This manuscript offers a methodology and examples for the estimation of time and cost savings based on MIDD-related activities at each stage of development across the entire drug development portfolio.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The value of MIDD is evident and increasing. The estimation of resource savings from MIDD approaches, using the methodology and examples highlighted in this manuscript, helps to further demonstrate its value in drug discovery and development and facilitates making MIDD a routine and expected practice in drug development.

The term model-informed drug development (MIDD) is used to describe the application of various quantitative models that leverage and integrate understanding of physiology, disease, and pharmacology to facilitate the decision-making process during drug development. MIDD is essential at each stage of the drug discovery and development process from nonclinical stages to regulatory submissions. The evolution of this field and the various stages in which MIDD can be applied to streamline the overall drug discovery, development, and regulatory evaluation processes have been well-documented.[1–7] Although a variety of terms such as model-based drug development (MBDD), model-informed drug discovery and development (MID3[1]), and quantitative pharmacology (QP) have been used to describe this approach, they all have the same underlying meaning.

At Pfizer, the implementation of MIDD over the last 2 decades has been described in a series of publications. In the first article,[8] Lalonde et al discussed the escalating costs of drug development and emphasized the application of model-based drug development

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as a tool to improve drug development. They described the key elements of model-based drug development (pharmacokinetics–pharmacodynamics [PK–PD] and disease models, competitor information and meta-analysis, design and trial execution models, data analysis models, quantitative decision criteria, and trial performance metrics) and provided examples illustrating the application of these key elements and positive impact on development programs. In the second article,[9] Milligan et al discussed the continued evolution of MBDD with particular emphasis on the requirements to implement and maintain the application of this concept within a large multinational pharmaceutical research and development organization. A series of illustrative examples was used to highlight the role that MBDD approaches play in accelerating and optimizing compound development strategies. In a more recent article,[10] Fediuk et al described the MIDD approaches used in the end-to-end development of ertugliflozin, a sodium-glucose cotransporter 2 inhibitor approved for the treatment of adults with type 2 diabetes mellitus. Model-informed approaches evaluating all available data were used to characterize the pharmacokinetics, dose proportionality, intrinsic/extrinsic factors impact, pharmacodynamics, efficacy, and drug–drug interaction potential of ertugliflozin. These analyses facilitated decision making, resulted in time and/or cost savings, and supported registration and labeling.[11]

Additionally, applications of MIDD have considerably evolved at the United States Food and Drug Administration (US FDA) since the earliest application in the 1990s when the US FDA Modernization Act (FDAMA) was signed into law.[12] Since then, efforts have focused on mainstreaming MIDD with an emphasis toward consistent review and decision making. Now, MIDD is recognized as one of the regulatory decision tools to support drug development and review as per the sixth iteration of the reauthorization of the prescription drug user fee act (PDUFA VI).[13] Most recently, the US FDA's Center for Drug Evaluation and Research (CDER) has established a new CDER Quantitative Medicine Center of Excellence with the goal of facilitating and coordinating the continuous evolution and consistent application of quantitative medicine across CDER and informing regulatory decision making.[14] Additionally, the International Committee for Harmonization (ICH) is also working on a new, overarching guideline on general principles for (MIDD) to broadly cover general principles and good practices for the use of MIDD in regulatory submissions.[15]

The application of MIDD has become an expectation at Pfizer, at some pharmaceutical companies and at regulatory agencies, and is used to support objective decisions,[16] thus having already proven its value. However, there is often the question about quantifying the value of MIDD in terms of resource savings across the portfolio. A consistent and complete estimation of value generated is difficult due to the multifaceted aspect of the efficiencies gained through its implementation. In the first year of implementation of model-informed study designs at Pfizer, the cost efficiencies gained over historical (typical) studies were estimated at about $70 million. Following 2 years of implementation, a reduction of $100 million was applied to the annual clinical trial budget in expectation of savings that would be realized through the application of these approaches.[1] While there are reports of cost savings such as the above at Pfizer and at other large pharmaceutical companies,[7,17] there has not been a comprehensive report on the impact of MIDD on a company's portfolio as measured by cost and time savings. Our objective was to systematically estimate the cost and time savings realized through the utilization of MIDD across the Pfizer clinical development portfolio.

MATERIALS AND METHODS

The systematic estimation of cost and time savings was enabled by capturing the MIDD plan (including potential impact to the program and decision making) as part of the clinical development plan document. The MIDD plan is a required component of the Clinical Development Plan (CDP), per standard operating procedures, that outlines the MIDD strategy at the given stage of development. The MIDD plan is a clinical team deliverable, and Clinical Pharmacology, Statistics, and Pharmacometrics & Systems Pharmacology leads drive the completion of the plan with key input from clinical and other lines as appropriate. For each model-informed analysis, the following information was captured: key development questions and decisions that are informed by the analysis, contributing data, key assumptions, risks and limitations, and impact to the development program focusing on the potential benefits (decreased risk, time, and increased efficiency) or potential impact if the analysis is not completed. The MIDD plan for each early (first-in-human to proof-of-concept [POC]) and late (post-POC) drug development program was reviewed, and impacts leading to cost and time savings were extracted. As MIDD-related cost savings and time savings are generally related to sample size reduction, waivers of clinical trials, and "No-Go" decisions for conducting a trial, a standardized method was used to estimate these savings.

For estimation of cost savings, Per Subject Approximation (PSA) values provided by the Portfolio Planning and Management group were used. These are default values derived from a sample of study cost averages based on Clinical Study Phase and Therapeutic Area (or healthy participant studies as applicable) that are used for early cost estimates for a study. As the PSA value provides the cost per subject, the total cost saving is calculated by multiplying the PSA value with the number of subjects for savings related to clinical trial waivers, "No-Go" decisions, or sample size reduction based on MIDD.

For estimation of time savings associated with MIDD-related waivers of Phase I studies, the typical time line from development of the protocol to the availability of the final clinical study report was used. The study time lines and average clinical trial budget estimates for typical Pfizer Phase I studies are presented in **Table 1**. For MIDD-related trial waivers or reductions in sample size for Phase II or Phase III studies, benchmark patient enrollment times and the number of sites initiated for various indications available from databases like the Centre for Medicines Research (CMR) database were used along with protocol and clinical study report development timelines to estimate time savings. For Phase I PK/PD studies in pediatric patients, benchmark enrollment times were not available within the CMR database, and therefore, enrollment times and trial budgets from recently conducted Pfizer Phase I pediatric studies were used to approximate time and cost savings (minimum timeline 36 months, average trial budget $4.5 M).

RESULTS

MIDD plans were reviewed for all active clinical development programs. These included 11 early development programs and 31 late development programs (including pediatric development and life-cycle management) spanning five therapeutic/disease areas. The algorithm demonstrated general applicability across the portfolio. Applying the methodology described above, MIDD-related time and cost savings were estimated for the portfolio, and the results are presented in **Table 2**. Overall,

Table 1 Study timelines and average clinical trial budget estimates for typical Pfizer Phase I studies

Study type	Number of subjects, site	Protocol to CSR timeline (months)	Average clinical trial budget ($)
Bioavailability/Bioequivalence	24, PCRU	9	0.5 M
Thorough QT	36, PCRU	9	0.65 M
Renal impairment	24, external CRU	18	2 M
Hepatic impairment	24, external CRU	18	1.5 M
ADME	6, external CRU	9	1.5 M
Drug–drug interaction	12, PCRU	9	0.4 M

CRU, Clinical Research Unit; PCRU, Pfizer Clinical Research Unit.

Table 2 MIDD-related time savings and cost savings for early and late development programs in the Pfizer Portfolio over a typical year between 2021 and 2023

Development stage	Number of programs (therapeutic area)	Time savings		Cost savings
		Overall (months)	Cycle time (months)	($M)
Late development	6 (Internal Medicine)	159	87	46
	8 (Inflammation & Immunology)	252	92	45
	5 (Oncology)	76	0	3.9
	7 (Rare Diseases)	15	6	0.7
	5 (Anti-infectives/Hospitals)	177	36	33
	31 (All TAs)	679	221	129
	Average Savings/Program	22	7	4.1
Early development	2 (Internal Medicine)	10	1	0.7
	2 (Inflammation & Immunology)	15	6	1.2
	4 (Oncology)	12	12	2
	2 (Rare Diseases)	8	8	0.5
	1 (Anti-infectives)	6	6	1
	11 (All TAs)	51	33	5.4
	Average Savings/Program	5	3	0.5
Total	42	730	254	134

Population PK and exposure–response analysis impacting pediatric programs produced the most substantial time savings (up to 4 years) by eliminating the need for dedicated Phase 1 PK/PD studies in pediatric populations or supporting dose recommendations for other age groups; these savings account for the overall months saved in Internal Medicine, Inflammation & Immunology, and Anti-Infectives/Hospital therapeutic areas.

for a typical development portfolio with approximately 50 clinical programs at a large pharmaceutical company like Pfizer, the use of MIDD yielded annualized average savings of approximately 10 months of cycle time and $5 million per program. MIDD analyses resulting in resource savings included population PK analysis, exposure–response modeling, physiologically based pharmacokinetic (PBPK) modeling, quantitative systems pharmacology modeling, and concentration-QT analyses. Of these, concentration-QT analysis impacted several programs in the portfolio, enabling the request of a waiver for a thorough QT study. Population PK and exposure–response analyses were also widely used, supporting large fold dose escalation and exploration of proof of mechanism in early development studies, elimination of region-specific studies, and enabling Phase III dose selection and final dose recommendation during registration. While PBPK models were commonly used in lieu of clinical drug–drug interaction studies, there was also one instance of using a PBPK model to obtain a waiver for a clinical bioequivalence study.[18] Among all applications of MIDD, population PK and exposure–response analysis impacting pediatric programs produced the most substantial time savings (up to 4 years) by eliminating the need for dedicated Phase I PK/PD studies in pediatric populations or supporting dose recommendation for various age groups. Additionally, while model-informed approaches eliminated the need for Phase I studies to assess drug interactions, the impact of organ impairment, QT prolongation, or bioequivalence, these rarely impacted development cycle times as these Phase I studies are often not rate limiting for a clinical development program. However, the elimination of these studies often made the Phase III programs more efficient. Development cycle times were significantly reduced for Phase II/III studies or elimination of Phase I studies for pediatric populations.

Regardless of time and cost savings, model-informed approaches facilitated decision making in every development program with regard to trial design, dose and regimen selection,

extrapolation to special populations, and reducing uncertainty. Some of the largest impacts of MIDD were related to "No-Go" decisions at the program level, which allow for reallocation of resources toward other programs with a higher probability of success; however, these impacts are difficult to quantify as time and cost savings.

Selected examples of MIDD analyses resulting in resource savings over the past few years within our organization are presented below.

Quantitative systems pharmacology (QSP) modeling to inform optimal timing of pharmacological interventions for the treatment of COVID-19

The development of novel therapeutics for the treatment of COVID-19 was challenging due to the complex pathophysiology of viral replication and the associated immune response. An integrated QSP model that captured viral dynamics, immune responses, and PK/PD of potential treatments in COVID-19 patients treated in clinical trials was developed.[19] The model predicted robust antiviral activity and indicated that the timing of intervention relative to symptom onset was critical. Model-based simulations of a virtual population treated with nirmatrelvir/ritonavir 300/100 mg BID predicted that 5 days of treatment are needed for robust viral reduction in patients with symptomatic COVID-19. There was no meaningful additional benefit predicted with longer dosing.

The immediate impact of this analysis was that a longer duration (10-day) arm/study was not conducted, resulting in a reduced number of patients and accelerated development. Additionally, by optimizing the timing of interventions, the model could help improve clinical outcomes for patients with COVID-19 and potentially help reduce healthcare costs associated with COVID-19 treatment.

Population PK modeling for extrapolation of the safety and efficacy of an antibacterial agent to pediatric patients

Ceftaroline is a broad-spectrum cephalosporin with in vitro activity against Gram-positive bacteria associated with cSSTI, including *S. aureus* (methicillin-susceptible and methicillin-resistant [MRSA] strains) and streptococci, as well as common nonextended spectrum β-lactamase–producing Gram-negative species.[20] Population pharmacokinetic modeling leveraging data across adult and pediatric indications was used (with regulatory agreement) in place of a previously planned prospective clinical trial to select ceftaroline fosamil high-dose regimens for pediatric patients aged > 2 months to < 18 years with complicated skin and soft-tissue infections (cSSTI).[21] These analyses enabled extrapolation of the expected safety and efficacy of the selected ceftaroline fosamil high-dose regimens for pediatric patients with cSSTI within a shorter timeframe than that required for a clinical trial. The estimated cost for a Phase II/Phase III clinical study in pediatric patients with cSSTI is at least $17 M and would need at least 5 years for execution from protocol development to final clinical study report.

This modeling approach was also utilized to assess the potential differences in cystic fibrosis (CF) patients.[22] The population pharmacokinetic model was leveraged to demonstrate the similarities in ceftaroline exposure for both adult and pediatric populations, which enabled regulatory approval and the addition of this patient population to the label.

Bayesian dose–response modeling in the design of a phase IIb study for an oral DGAT2 inhibitor alone or coadministered with a liver-targeted ACC inhibitor in adults with NASH

A Phase IIb, dose-ranging, dose-finding, 9-arm, parallel group study (trial registration number NCT04321031) was conducted to evaluate histological endpoints after oral administration of diacylglycerol acyltransferase 2 inhibitor (DGAT2i) and DGAT2i + acetyl-coenzyme A carboxylase inhibitor in participants with biopsy-confirmed nonalcoholic steatohepatitis and fibrosis stage F2 or F3. Sample size estimation for this study was driven by the characterization of dose–response and drug effect using a Bayesian maximum effect of drug (E_{max}) study design and modeling approach, which utilized weakly informative priors for model parameters.[23] This approach increased the precision in drug/dose comparisons and enabled the required sample size to be reduced by almost half compared with conventional pairwise comparisons. The Bayesian dose–response modeling also enabled an efficient and complete characterization of dose–response to aid Phase III dose selection. The reduced sample size resulted in an estimated savings of approximately $25 M and potentially decreased enrollment time by approximately 6 months (based on a NASH patient enrollment rate of 1.35 patients per month).

Use of single-dose escalation study, PK/PD modeling, and a Bayesian adaptive Phase Ib/Phase II study to expedite early clinical development of marstacimab

To inform and accelerate the development of marstacimab (a human monoclonal antibody [mAb] that targets tissue factor pathway inhibitor (TFPI) to increase clotting activity in patients with hemophilia), a single dose escalation study in healthy subjects[24] was leveraged along with PK/PD modeling to support dose selection and the decision to progress to a Phase Ib/II seamless adaptive study (NCT02974855) in severe hemophilia patients.[25] The study was not placebo controlled (instead comparing bleed rates in the 6 months before and the 6 months on study) and used historical annualized bleeding rate data incorporating historical priors using a Bayesian approach and comparative efficacy to set a priori target value to take a go-no-go decision for the study based on the first cohort enrolled. With a Bayesian adaptive design, the study enrolled the dose with a higher probability of success first, and after providing a sign of robust clinical activity, adapted to fill the higher and lower part of the dose response (delivering proof of concept and dose selection for Phase III). Overall, this strategy along with the quantitative analysis enabled the entire early development to be executed with two studies involving only 41 healthy participants and 26 severe hemophilia patients, drastically expediting the development process (development timeline reduced by 18 months) and potentially giving an opportunity to get transformational therapy to patients faster. Marstacimab has since completed Phase III development.

PBPK modeling to assess DDI potential in lieu of a clinical DDI study

As the primary route of clearance for ertugliflozin (a sodium-glucose cotransporter 2 inhibitor for the treatment of type 2 diabetes) is glucuronidation via the uridine 5′-diphospho-gluc uronosyltransferase (UGT) isoforms UGT1A9 and, to a lesser extent, UGT2B4 and UGT2B7,[26–28] it was important to assess the potential for DDIs between ertugliflozin and UGT enzyme inhibitors. The UGT-mediated DDI for ertugliflozin in humans was assessed using PBPK modeling and mefenamic acid as the UGT inhibitor.[29] Physiologically based pharmacokinetic (PBPK) modeling utilizes a mathematical model to simulate the pharmacokinetics of a drug over time by considering the absorption, distribution, metabolism, and excretion (ADME) properties of a drug and the interrelationship between the physiological and chemical determinants of the disposition of the drug. The simulation predicted a weak DDI between ertugliflozin and mefenamic acid, with an AUC ratio of 1.51 (95% CI: 1.48–1.54) and C_{max} ratio of 1.19 (95% CI: 1.17–1.20); this DDI was not considered clinically relevant. The ertugliflozin PBPK model-based DDI results were included in the ertugliflozin regulatory submission and the results incorporated into the DDI section of the label[11] without the need for a clinical DDI study with a UGT inhibitor. The estimated cost for a typical 2-period, single-sequence clinical study to evaluate such a drug–drug interaction in 12 healthy subjects is at least $0.4 M, and would need approximately 9 months for execution from protocol development to final clinical study report.

Use of virtual control cohort in organ impairment studies

In special population studies, a reference healthy participant (HP) cohort with matching demographics to the organ-impaired groups is typically enrolled to understand the impact of organ impairment on the PK of a compound. When the recruitment of healthy participants for such a control group for evaluation of organ impairment on ritlecitinib PK posed a challenge during the COVID-19 pandemic, an MIDD approach based on a POPPK model developed using available data at the time of the analysis was used.[30] The model characterized the PK of ritlecitinib leveraging random sampling, uncertainty of exposures in HPs, and simulation of multiple matched HP cohorts to generate a distribution of possible outcomes, thus providing a more robust estimation of the difference between populations than a traditional matched cohort study, as it used data from a larger number of HPs than typically recruited for organ impairment studies. Simulations based on this POPPK model adequately represented the distribution of exposures that could be expected in an HP cohort. Relative to a traditional study design, in which a single HP cohort reference represents a random sample of 1, the simulation approach can generate thousands of reference groups, providing a more complete assessment of the likely distribution of the geometric mean ratio. The estimated cost for a typical healthy participant cohort for such studies is at least $0.25 M and would need at least 3–6 months for recruitment.

Automation of MIDD analyses: Automated monitoring of Phase I studies and CardioERMs

Two examples of time and resource saving automation tools are the Automated Monitoring of Phase 1 (AMP) tool and CardioERM (Cardio Exposure–Response Modeling). AMP was developed to enable quick and easy monitoring and validated review of safety, tolerability, PK, and PD data for any Phase I study conducted at a Pfizer Clinical Research Unit. The typical timeline for data review was 4 business days (to final tables and figures), while AMP is able to process this within a few minutes. Assuming five dose escalation periods per ascending dose study and a minimum of 10 such studies per year, the time savings are estimated at about 200 business days per year.

Assessment of QT liability is important for all new molecular entities in drug development. A typical analysis, based on a recent white paper[31], may take up to 1–2 months for analysis planning, data review, execution, report writing, and associated QC review. An automated tool, CardioERM, was developed to efficiently assess drug concentration and QT relationship, provide logical interpretation of results (eg assessment for hysteresis assumption), and generate a regulatory-ready report in only a few minutes. The report is the quantitative technical document underpinning a waiver for QT monitoring Phase III. The compression of the time and resources captures up to 60 business days for each analysis, and when applied to 5 programs per year, a time savings of 300 business days would be expected.

DISCUSSION

To our knowledge, there has not been a comprehensive report on how MIDD impacts a pharmaceutical company's portfolio in terms of cost and time savings. Our goal was to systematically estimate the cost and time savings achieved by using MIDD across the Pfizer clinical development portfolio. The analyses presented in this publication led to a few key insights: More savings occurred in late development than in early development (probably because of the larger size and number of trials that could benefit from MIDD savings in late development). This may also explain why more savings were realized in non-oncology therapeutic areas than in oncology. However, there is potential for improvement as the MIDD savings could apply to post-marketing commitment phase in oncology where it is not widely used yet. Also, MIDD savings appeared to be at steady state for Internal Medicine, Inflammation and Immunology, Anti-infective/Hospital, and Rare Disease therapeutic areas. However, with Project Optimus for Oncology[32], there is more awareness of the need for dose optimization, which will increase the demand for MIDD in oncology. MIDD savings were realized for all drug modalities, and a more thorough analysis is needed to identify typical savings realized based on the different development pathways for the different modalities. Lastly, there were no clear examples of negative savings (i.e., where using MIDD resulted in repeating a study, losing a claim). While there may have been cases where this happened during development, it did not appear to affect overall development cycle times.

As the MIDD plan is a required component of the CDP, incorporation of model-informed approaches is built into the

development path at Pfizer, and inter-disciplinary project teams routinely engage with MIDD scientists for their input as the CDP is drafted.

There are different ways to characterize savings in clinical programs. More objective types of savings are related to a colleague's time, the number of participants in a trial, and specific components of clinical trial endpoints (e.g., number of PK samples being collected). In areas where automation or other types of efficiency (e.g., templates, generative-AI enabled process, etc.) are achieved, the colleague time saved can be calculated for each of the underlying processes (data manipulation, analyses, report writing, and QC) multiplied by the associated cost. While this can be perceived as cost savings, it is also a way to enable the quantitative scientists to focus more time on more complex analytics which may not have been possible due to the amount of time needed for more routine assessments. The number of participants in a clinical trial can be reduced using a Bayesian prior, or in other cases where those subjects can be appropriately simulated. Components of clinical endpoints (number of PK samples or biomarkers) all have associated costs for analysis. Utilizing a model to reduce the number of samples being collected, or types of samples being collected, can lead to a clear calculation of savings (number of samples saved × cost per sample). The direct cost savings are determined by the number of participants or number of samples not needed for the study leading to a clear cost per participant and number of participants, while the indirect savings can be observed on time to decision.

While these are all objective savings, the subjective savings should also be factored into the overall calculations. Examples of subjective savings are cases in which MIDD is used to make an informed decision earlier in a clinical study to either accelerate or terminate the program. For this assessment of MIDD savings, subjective savings were not estimated or included. However, the quicker an informative program decision can be made, the faster the time to registration leading to significant revenue gains due to earlier market entry and an extended period of exclusivity, which could also be counted as cost savings.

As MIDD becomes standard business practice with recurring assessments being performed across the development lifecycle,

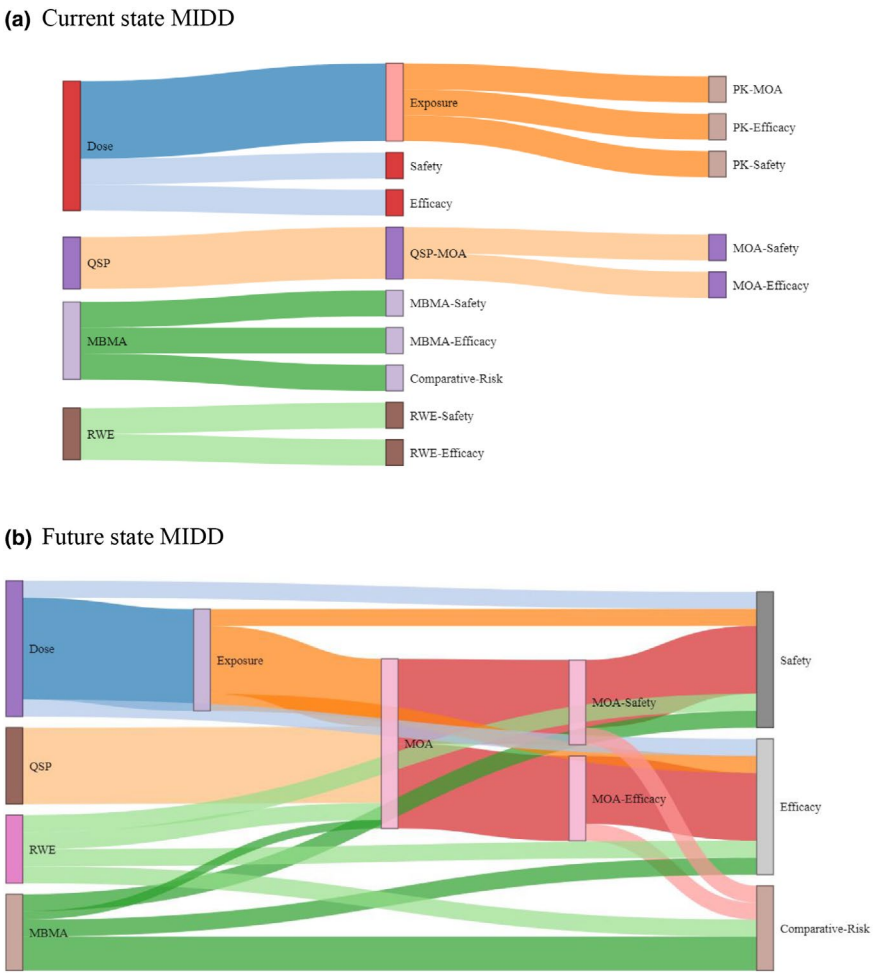

Figure 1 Current and future state representation of a model-informed drug development (MIDD) dynamic communication interface. The alluvial diagram is constructed of nodes and linkages. Nodes are a state of quantitative knowledge for an area. Linkages are the analyses (quantitative relationships) between nodes. The current state (**a**) depicts work in parallel that may interconnect through manual interpretation. The future state (**b**) depiction integrates the different modalities into a unified (holistic) interface. Clinical trial simulations would be enabled for each node or combination of nodes to interrogate future clinical questions (e.g., changing dosing regimen, different formulation characteristics, changes in patient characteristics).

automation, or more rapid analytics become necessary. The question being addressed by a specific analysis may change during program development, though the underlying need to inform internal decisions and regulatory interactions is consistent. To maintain momentum, program decisions are often made proximal to the completion of a study at the time of a top-line report. Any analysis that is not available at this time, no matter how well done, loses its impact on decision making and is considered a reassessment of the original decision if considered at all. Therefore, it becomes imperative to enable MIDD analytics, with embedded quality and associated documentation, to be available at the time of decision making.

Automation of analyses and reporting is a first step in being able to impact rapid decision making. This has already been accomplished for more typical model types (e.g., concentration-QTc analyses) in which a standardized dataset is processed by a myriad of scripts and finally produces a report ready for regulatory interaction. In many cases, more complex models are being implemented. As the model structure is being explored, the model process may not be suited for automation, though the overall workflow (data exploration, table and figure generation, diagnostics, and reporting) can be. This current state of MIDD has enabled quantitative influence on the decision making. The ability to have information analyzed as it is collected, in real time, is a logical next state for much of the MIDD work being applied to study analyses. This real-time analytic approach will stem from sample collection and reconciliation through to exposure and exposure–response analyses. The efficiency gained from furthering automation would be expected to drive greater savings, thus fulfilling our mission to bring medicines to patients faster.

For models characterizing information from literature or other non-study databases (model-based meta-analysis (MBMA), QSP, real-world evidence (RWE)) analytical outputs would be generated prior to or in parallel to an ongoing clinical trial. These would be expected to aid in the integration of clinical trial information within the larger quantitative understanding of the disease area, risk, and benefit. Such non-study data may be used to validate the assumptions and predictions made by study data-based models, assessing how well the model reflects real-world patient populations. However, while RWE/RWD/AI and other non-study data sources are expected to further guide and generate MIDD-related savings, the cost of access to these datasets may offset net savings.

The future state will need to enable a holistic integration and dynamic representation of MIDD (see **Figure 1**). Here, the output of models describing safety, biomarkers, efficacy, etc., will be linked as modular objects to the exposure of compound. This holistic interface would also incorporate the quantitative understanding of disease state (QSP, disease progression, natural history models, etc) and competitive landscape (MBMA). As each of these models is updated throughout their respective lifecycles (MDLC) so would the holistic application. Each updated MDLC version would also enable clinical trial simulation for study design. This application, or linked series of applications, represents the quantitative knowledge for the program, mechanism of action, and indication. By integrating all of the information, MIDD will enable quantitative decision making at all levels of the program (dose rationale to target product profile) and probability of success (PTV, PTS, & PTRS) estimations. This type of holistic application would also enable more efficient regulatory interactions, as questions on dosing, populations, disease burden, etc., could be rigorously interrogated for not only impact on drug exposure but also what that change in exposure translates to in terms of benefit-risk. Finally, this holistic composition of models in a dynamic application could be made available to clinicians and external investigators to help guide dosing to support further clinical trial design.

In summary, this analysis demonstrated that implementation of MIDD delivered significant time and resource savings when measured across an entire portfolio. The methodology was capable of quantifying the value in a systematic and consistent manner across the entire Pfizer portfolio, and could be applied across a variety of types of analyses and at various stages of development. Value was captured as time savings and accrued costs. With the incorporation of the MIDD plan within the CDP that is routinely reviewed by governance bodies, the practice of MIDD has become "business as usual" at Pfizer. The impact on development cycle times was substantial (ranging from 6 months to 4 years) and resulted in availability of medicines to the patient sooner.

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CONFLICT OF INTEREST

VS, TN, GN, and CJM are employees of Pfizer and may own stock in Pfizer. BC was an employee of Pfizer at the time the manuscript was drafted.

AUTHOR CONTRIBUTIONS

V.S., T.N., G.N., C.J.M., and B.C. wrote the manuscript, designed the research, performed the research, and analyzed the data.

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