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A Framework for Incorporating Model-Informed Drug Development (MIDD) into Decisions for Selecting the Registrational Dosage in Oncology Drug Development

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Executive Summary

Optimizing the dosage in oncology clinical trials requires balancing efficacy, safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), patient experience, and relevant nonclinical evidence. FDA's Project Optimus emphasizes moving beyond a default maximum tolerated dose approach toward selecting a dosage that provides the most favorable benefit-risk profile. However, clinical evaluation of multiple dosages can be resource-intensive, might expose patients to dosages that offer limited benefit or unacceptable toxicity, and may not fully address increasingly complex dosing questions. Model-informed drug development (MIDD) provides an opportunity to integrate diverse sources of evidence, quantify uncertainty, and support more efficient dosage optimization.

Although MIDD's role in regulatory review of marketing applications is increasingly established, its role during the investigational new drug (IND) phase, when dosage optimization and registrational dosage selection occur, is less well defined. Greater clarity regarding how to appropriately incorporate MIDD into the totality of evidence of dosage decisions could help sponsors design more efficient development programs, reduce unnecessary clinical evaluation, reduce patient risk or harm and improve confidence in the selected dosage.

Friends of Cancer Research convened a multidisciplinary working group to develop a framework for incorporating MIDD into oncology dosage optimization and selecting the registrational dosage. Building on principles from the International Council for Harmonisation (ICH) M15 guidance, the framework provides recommendations for using MIDD in dosage selection through four steps: (1) defining the question of interest, (2) selecting the appropriate context of use and MIDD approach, (3) evaluating the risks and credibility of relying on model-informed evidence, and (4) integrating MIDD findings with the totality of evidence.

Recommendations focus on a variety of challenging dosage decisions:

- Limited differentiation between candidate dosages
- Intermediate dosage selection
- Dosing regimen optimization
- Exposure variability based on patient characteristics
- Combination therapy dosages
- Extrapolating into different cancer types

Emerging approaches and data sources, including clinical utility indices, patient-reported outcomes, real-world data, digital twins, and artificial intelligence/machine learning, may further expand the ability of MIDD to integrate evidence and inform dosage decisions. Continued collaboration among regulators, industry, academia, clinicians, and patients will be important to generate regulatory experience, clarify expectations for model credibility, and establish best practices for integrating MIDD with clinical evidence. Collectively, these efforts can support a more consistent, transparent, and risk-based approach to oncology dosage optimization and selection of dosages that provide the most favorable benefit-risk profile for patients.

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Introduction

The U.S. Food and Drug Administration's (FDA) Project Optimus emphasizes that oncology *dosage*[*] selection should be based on an integrated assessment of clinical efficacy, safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), patient experience, and relevant nonclinical evidence to identify the optimized *dosage* for patients rather than defaulting to the maximum tolerated *dose*. Identifying the optimized *dosage for registrational studies* requires a series of decisions throughout the early stages of oncology drug development. Preclinical assessments and quantitative translational approaches such as PK/PD modeling and *quantitative systems pharmacology (QSP)* inform selection of the first-in-human (FIH) dose, which is then evaluated in patients using a prespecified escalation and toxicity monitoring plan. Based on emerging safety, PK/PD, clinical activity, and tolerability data from dose escalation, candidate dosages may be subsequently evaluated in dose optimization cohorts, ideally providing sufficient exposure separation to inform benefit-risk comparisons. FDA guidance recommends incorporating randomization into dose-finding studies with two or more candidate dosages.[1] Dosage randomization may be considered even when patient populations are limited. Streamlining evidence generation can help sponsors generate robust information over multiple dosages while ensuring timely patient access to therapies and minimizing exposure to dosages that are unlikely to provide meaningful clinical benefit, that may cause short or long-term toxicities, or that offer no additional benefit over a lower, better-tolerated dosage.

Model-informed drug development (MIDD) quantitatively integrates the totality of evidence for dosage selection and facilitates decision making. When applied in a fit-for-purpose manner, MIDD can help improve the efficiency of evidence generation. MIDD approaches may help reduce unnecessary patient exposure, trial burden, and development timelines while preserving confidence in the selected dosage.[2,3] However, effective application of MIDD can be constrained by practical considerations related to data, information, domain knowledge availability, model assumptions and complexity, as well as development and decision-making timelines. Uncertainty about how MIDD will be considered as part of the dosage selection package may lead sponsors to pursue additional, and sometimes unnecessary, clinical studies. In some cases, sponsors may conduct parallel dosage optimization efforts across multiple cancer types rather than rely on extrapolation supported by MIDD, particularly when the acceptability of model-informed evidence is uncertain.

The FDA's Office of Clinical Pharmacology's Issue Based Review framework incorporates MIDD into regulatory review of new drug applications and biologics license applications.[4] However, the role and importance of MIDD approaches during the investigational new drug (IND) phase, when dosage optimization occurs, is less well defined. Although recent FDA guidance outlines general principles for assessing and applying MIDD from the International Council for Harmonisation (ICH) M15 guidance titled "General Principles for MIDD,"[5] and the more recent draft FDA QSP-MABEL guidance builds on M15 for an early FIH dose selection,[6] additional clarity is needed regarding the appropriate role of different modeling approaches and model performance requirements, the evidentiary standards required, and the circumstances in which clinical data remain indispensable for dosing decisions. Together, these clarifications could support sponsors in decision-making for their approach to dosage optimization and selection.

[*] The first use of a word in the glossary is italicized and underlined in the text.

Friends of Cancer Research established a working group of experts to explore how the use of MIDD supports more efficient, evidence-based dosage optimization in oncology drug development, and how principles from the M15 guidance can inform the identification and justification of the appropriate model based on the question of interest. We specifically focus on challenging questions such as evaluating dosage in different lines of therapy, across indications, and in combination therapies. For each question of interest, we outline considerations for integrating MIDD into oncology dosage optimization, with an emphasis on selecting the dosage used for registrational studies and exploring emerging approaches for MIDD to support dosing decisions. We focus on key information and discussions that will be most impactful for drug developers, investigators, patients, patient advocates, and regulators.

This white paper is one of three complementary Friends of Cancer Research publications exploring opportunities to modernize early-phase oncology drug development through more efficient, evidence-based approaches that maintain patient safety.[7,8]

Framework for Incorporating MIDD into Dosing Decisions

The goal of this framework is to provide recommendations for identifying which MIDD tool(s) can support the selection of the registrational dosage and how these tools can inform dosing decisions as part of a totality of evidence by building on the M15 guidance framework.[5] Proactive planning and efficient integration of appropriate MIDD approaches into the Model Analysis Plan, as an integral part of the overall development plan, is recommended, particularly in areas where conducting intensive clinical evaluation is impracticable (e.g., pediatrics, rare disease). However, some analyses cannot be pre-defined as they depend on emerging data. Our framework focuses on general principles for using MIDD to select the registrational dosage rather than providing modality-specific information; representatives from the FDA recently published case examples of incorporating MIDD into dosing decisions across different modalities.[9]

Step 1. Question of Interest: What dosing decisions would MIDD help answer?

As a development program progresses through dosage optimization, outstanding questions may remain despite robust clinical data. In the following scenarios, MIDD could fill evidence gaps by characterizing uncertainty and helping determine whether or what additional clinical data would meaningfully change the overall understanding of the benefit-risk profile. MIDD could support an understanding of whether generating additional clinical evidence would support dosage selection. Examples are limited as much of the modeling occurs during the IND phase.

- Limited differentiation between candidate dosages: Candidate dosages may yield overlapping exposure distributions, making it difficult to determine which two dosages to evaluate in a dose-finding study. Alternatively, there may be a limited number of patients, insufficient follow-up, or potential imbalance in baseline factors that affect response, leading to limited differentiation. MIDD can help account for variability and confounding factors to better to characterize the underlying dose-response relationship. MIDD can also help predict the number of patients at each of the dosages that are likely to be in the efficacious and safe dose range, accounting for variability in PK to support selecting one dosage versus the other to test in a registrational trial. In situations with precedented mechanisms of action, there may be class-specific data that could be used in MIDD. Additionally, MIDD may be used to assess whether the expected differences between dosages are sufficiently large to be detectable in a planned clinical study of feasible size and duration, and whether additional dose-finding evaluations are likely to substantially reduce uncertainty.

- Intermediate dosage selection: Sometimes, the clinically evaluated dosages bracket the desired benefit-risk balance (e.g., lower activity at one dosage and increasing toxicity at the other). When early clinical data suggest the evaluated dosages have non-overlapping risk-benefit profiles, MIDD may support evaluation of an intermediate dosage by predicting its exposure and interpolation of expected efficacy and tolerability; this may build confidence in moving forward with an intermediate dosage for which direct clinical data are limited, allowing for a more optimal benefit-risk balance.
- Dosing regimen optimization: In settings where the dose level is clearly identified but the regimen may still need adjustment, MIDD may inform alternative dosing schedules or demonstrate that alternative dosing schedules do not meaningfully change the benefit-risk assessment. For therapies in which benefit and toxicity depend on cumulative and temporal exposure, MIDD may enable simultaneous evaluation of dose per administration, dosing interval, treatment duration, number of doses, front-loading, and dose adaptation rather than treating each parameter independently. This may be particularly valuable for therapeutic modalities such as radiopharmaceuticals, antibody drug conjugates (ADCs), bispecific T-cell engagers, or other treatments in which benefit and toxicity depend on both cumulative and temporal exposure (e.g., therapies exhibiting hematological adverse events). For radiopharmaceuticals, optimization and MIDD approaches should also consider administered activity, treatment interval, number of cycles, cumulative activity, and dose adaptation.[10]
- Exposure variability based on patient characteristics: Dosages may need to be adjusted for certain populations based on clinical characteristics (e.g., renal or hepatic function) or genotype differences in drug disposition (e.g., polymorphisms in CYP2D6 enzyme). Biomarker-defined characteristics, including target expression, receptor occupancy, molecular subtype, pharmacodynamic biomarkers, or other predictive markers, may also modify exposure-response relationships and therefore inform dosage selection or stratification. In some cases, this may be due to genetic alterations impacting efficacy of the therapy.[11] Pediatric populations especially require additional dosage optimization for therapies used in adult patients. MIDD can help characterize how these factors influence drug exposure and inform dosage adjustments for specific patient populations.
- Combination therapy dosages: When developing combination regimens, there are two important questions: dosage optimization of each component within the combination and contribution of individual components to the treatment effect.[12] Here, we focus on how MIDD can be used to select the appropriate dosages for the treatments included in the combination. When therapies are administered in combination, data from individual components and small sentinel or run-in cohorts often support dosage decisions for dose-finding trials and/or the registrational trial. Because components may be administered at different dosages in combination than as monotherapies, MIDD can support dosage decisions for both novel-novel and novel-approved combinations.[10] Additionally, MIDD can evaluate PK interactions, PD interactions, combination drug dosage optimization, and sequencing. MIDD may also contribute to the totality of evidence to support demonstration of the contribution of components when dosages are different than those administered as monotherapies.
- Extrapolating into different cancer types: Oncology drugs are often initially approved for a single cancer type, then expanded into other cancer types. Datasets in novel cancers may be limited and increasingly complex due to evolving standards of care and the growing use of combination regimens rather than single-agent therapies. Extrapolating dosage selection across tumor types is

an important future application of MIDD, but current approaches and evidentiary standards remain relatively immature. It will be critical to consider how population-specific factors affect dosage selection with changing tumor types (i.e., moving from non-small cell lung cancer to hepatocellular carcinoma or relapsed refractory to smoldering multiple myeloma).

- Changes in disease states: Cancer therapies are often initially developed for patients with the most advanced disease, who have already received multiple prior lines of other therapies. The benefit-risk considerations for the therapy may change as therapies are developed for earlier lines or in maintenance or adjuvant settings, which may result in necessary updates to the dose, frequency, or duration of administration. MIDD may support decisions about dosages as therapies move into earlier lines of therapy and earlier stages of cancer.

Step 2. Context of Use: Which model(s) answer the question of interest?

For each context of use, it will be critical to assess available nonclinical and clinical data to support the totality of evidence as well as which data inform selection of the most appropriate model.[13] An overview of MIDD tools and the data they incorporate and provide is included in the Appendix Table.

Tools include:

- *Exposure-response analyses (E-R analyses)* E-R
- PK/PD PK/PD
- *Population pharmacokinetics (PopPK)* Pop PK
- Longitudinal PK/PD models for safety and efficacy Long PK/PD
- *Tumor growth inhibition- overall survival/ progression free survival (TGI-OS/PFS) modeling* TGI OS
- *Disease progression modeling (DPM)* DPM
- Time-to-event models (TTE; e.g., first dose modification such as dose reduction or delay or progression) TTE
- QSP QSP
- *Physiologically Based Pharmacokinetic (PBPK) modeling* PBPK
- *Model-based meta-analysis (MBMA)* MBMA

Tools should be tailored to the development program and context rather than used in the same way for every scenario. Selection of a MIDD approach should be guided by whether the model is fit-for-purpose for the specific decision, clinical context, available data, and level of uncertainty that remains. Table 1 provides recommendations for which MIDD tool(s) can answer each question and how the data output from the tool might be interpreted. Multiple tools can answer the same question depending on the timing of development and available data.

Table 1. Questions of Interest and MIDD Tool(s) to Consider

Question of Interest	MIDD Tool(s)	Interpretation
Limited differentiation between candidate dosages	• E-R-safety/ efficacy E-R • PK/PD PK/PD • TTE-Tolerability TTE	• Shows exposure margins between minimum effect exposure and the exposure associated with unacceptable toxicity or tolerability. • Provides quantitative measure of uncertainty around exposure-efficacy and exposure-safety relationships and tolerability across the exposure range; assesses likelihood of clinically meaningful differences between dosages adjusting for confounding factors
Intermediate dosage selection	• E-R safety/ efficacy E-R • PK/PD PK/PD • TGI-OS TGI-OS • QSP QSP	• Simulates the expected benefit-risk profile for an intermediate dosage which has limited or no clinical data
Dosing regimen optimization	• E-R E-R • PopPK Pop PK • Longitudinal PK/PD • QSP QSP	• Simulates the expected exposures under alternative dosing schedules against the current one • Informs whether a regimen change preserves or improves the outcomes • Simulates longitudinal data across dosage regimens to identify schedules with a more favorable therapeutic index
Exposure variability based on patient characteristics	• E-R E-R • PopPK Pop PK • PBPK PBPK	• Informs whether dosage should be adjusted based on certain patient characteristics or extrinsic factors such as change in meal conditions

Question of Interest	MIDD Tool(s)	Interpretation
Combination therapy dosages	• E-R • PK/PD • PopPK • Translational PK/PD • QSP	• Integrates multidimensional evidence to identify a range of dosages that meet efficacy/toxicity parameters (visualized as a "surface") • Models individual components' impact on toxicity • Informs sequencing (e.g., TCE prior to ADC or dosing them simultaneously) of combination • Rank orders various dosing regimens based on totality of data for early clinical evaluation
Extrapolating into different cancer types	• E-R • PopPK • Translational PK/PD • QSP	• Informs exposure comparability of the same dosage in the new disease setting or a different patient population • Assesses whether PK and E-R relationships are sufficiently transportable across disease settings or populations
Changes in disease states	• QSP • DPM	• Simulates the underlying natural progression of a disease and its response to treatment over time, emergence of mutations, disentangling natural progression from drug effect and informing useful biomarkers • Evaluates differences in baseline target expression
	• MBMA	• Evaluates baseline safety • Addresses efficacy, longitudinal data, and dose-response relationships from multiple clinical trials

Abbreviations: E-R, Exposure-Response; TGI- OS, tumor growth inhibition overall Survival; PopPK, population pharmacokinetics; PK, pharmacokinetics; PD, pharmacodynamics; QSP, quantitative systems pharmacology; DPM, disease progression modeling; TCE, T-cell engager; ADC, antibody-drug conjugate

Step 3. Potential Risks: What risks are associated with relying on a model for dosing decisions?

Step 3 encompasses four elements of the M15 guidance: model influence, consequence of wrong decision, model risk, and model impact. Many of these risk decisions are broad and should be considered when evaluating and using MIDD in dosage optimization. There are also risk considerations specific to dosage optimization.

The degree of confidence needed to support the decision and the residual uncertainty that may require additional clinical data should be established. In this regard, the level of model evaluation and evidentiary support needed should consider the influence of the MIDD evidence on the dosage decision and the consequence of an incorrect decision. Greater confidence may, for example, be required when model-informed evidence is used to support a dosage or regimen not prospectively evaluated in a clinical comparison than when modeling supplements an otherwise robust clinical dose comparison. This could distinguish circumstances in which MIDD: 1) supplements clinical dose-comparison data; 2) reduces the amount of additional clinical evidence required; or 3) provides sufficient evidence to support a dosage/regimen that has not been directly compared prospectively.

Remaining residual uncertainty can stem from the model credibility, which is driven in part by biological plausibility, data integrity and model fidelity. Model credibility should follow a risk-based evaluation approach similar to that laid out in the M15 guidance.[5] Transportability and generalizability of model inputs across regions and populations should consider regional differences in clinical practice as well as physiological or ethnic sensitivity differences in patient populations.

For dosage decisions, model applicability also depends on whether the underlying data are relevant to the current context of use, sufficiently mature, representative of the intended population, and adequate to support the model parameters driving the decision. For example, sparse early sampling may limit confidence in absorption-related parameters, limited dose or exposure ranges may constrain E-R analyses, and underrepresentation of relevant patient subgroups may limit evaluation of covariate effects. These limitations should be described transparently, along with their implications for the proposed dosage decision.

Step 4: Totality of Evidence: How are MIDD findings considered as part of the totality of evidence?

MIDD findings should be interpreted alongside the totality of available evidence, including observed clinical safety, efficacy, tolerability, PK/PD, and patient experience, as well as relevant nonclinical and prior knowledge of disease area and class effects for drugs with precedented mechanism of action. Together, these evidence sources can contextualize model-based findings and inform dosage and development decisions. The key question is whether the model-informed evidence meaningfully reduces uncertainty for the dosing decision being made and whether the findings are consistent with, complementary to, or not aligned with other available evidence. Any assumptions and limitations should be clearly stated and communicated with the model outcomes.

While MIDD offers opportunities to integrate totality of clinical data, there are also limitations of the tools due to data constraints and uncertainties in model assumptions. Data issues include lack of sufficient dose or exposure range, immature efficacy outcomes and limited follow-up, patient dropout due to toxicity or disease progression, or data quality issues. Modeling results may sometimes prove inconclusive, whether

conflicts between MIDD outcomes and actual data or discordance in results across different MIDD approaches. Outputs may be confounded by relationships among dose, exposure, prognosis, and dose modification, or it may be challenging to understand the application of commonly modeled early endpoints (i.e., overall response rate, biomarkers) to long-term outcomes (i.e., PFS, OS) and associated translational gaps. A model can provide actionable insights, but critical gaps in clinical development plans may potentially limit the reliability and value of these predictions.

Emerging Opportunities

Clinical Utility Index and Multiattribute Frameworks

Model-informed approaches can support dosage optimization by integrating multiple efficacy and safety endpoints into a single quantitative framework. Clinical utility index (CUI) and related clinical utility score (CUS) approaches combine model-predicted outcomes across clinically relevant attributes using prespecified utility functions and weights for individual endpoints, allowing different dimensions of benefit and risk to be considered simultaneously. An exposure-response-based CUS framework can apply model-predicted outcomes across multiple oncology development programs and identify exposure ranges corresponding to recommended doses or incorporate different endpoints to assess the overall benefit-risk profiles of different dosing levels.[14–16] These approaches provide a quantitative means of incorporating the totality of available evidence and making the relative importance assigned to different endpoints explicit. Importantly, the weighting of endpoints should be prospectively justified and evaluated through sensitivity analyses, as different assumptions about the relative importance of efficacy, safety, tolerability, or other outcomes may influence the resulting dose selection.

Incorporating Data into Models

As models become more sophisticated, there may be opportunities to incorporate additional data elements to support a clearer understanding of the different dosages and use data sources not traditionally incorporated into models. There are emerging opportunities related to integrating novel data types, AI-derived features, or real-world data into MIDD frameworks.

Patient Reported Outcomes (PROs)

Incorporating PRO data into dosage optimization decision-making is an evolving concept. PROs can help distinguish treatment-related symptoms from disease symptoms, incorporate repeated measures to assess changes from baseline at different relevant timepoints rather than a single deterioration timepoint, and examine exposure relationships with symptom severity and functional interference. While incorporating PROs into modeling is less common than other clinical measurements or endpoints, exposure-PRO relationships may inform dose modifications that improve adherence and tolerability.

A recent framework provides recommendations for incorporating PROs into dosage optimization, highlights practical considerations for PRO collection in early oncology development, and proposes a novel evidence-integration framework in which PRO data are visualized alongside efficacy, safety, and pharmacology data to support informed dosage optimization decisions.[17] Due to the nature of the data, there may be limitations related to sample size, the potential for patient burden and resulting missing data, and the ability to extrapolate data to broader populations. PRO data would most effectively contribute to dosage optimization when the instrument and timing are selected prospectively to evaluate treatment burden across dosages.

Real-World Data (RWD)

RWD can be included to characterize disease natural history to establish benchmarks, complement trial data where evidence is limited (e.g., earlier lines of therapy, adjuvant settings), support time-to-event analyses as additional input for E-R modeling, and address missing data gaps. For drugs that are already approved for other indications, RWD can be incorporated into MBMA during dosage optimization to estimate whether the proposed registrational dosage has a better probability of performing favorably, compared with alternative dosages, relative to the standard of care arm. When incorporated into an MBMA framework, RWD can help characterize disease natural history, establish external benchmarks, quantify treatment-effect expectations in specific patient populations, and refine probability of success estimates at the selected dose. RWD can inform covariate distributions that feed into QSP or other MIDD tools when switching between indications. Data quality, confounding information, and generalizability across regions are all important to consider when using RWD.

Digital twins represent an emerging modeling approach, leveraging patient-specific RWD to create virtual, mechanistic replicas of an individual's biology, organs, and disease states. They can be continuously updated and simulate drug absorption, distribution, metabolism, excretion, and response, which could enable optimization of dosing regimens prior to administration. QSP-based digital twin approaches can complement E-R analyses by using mechanistic models to simulate E-R relationships across heterogeneous patient populations to characterize the dose and identified potential pretreatment biomarkers predictive of response.[18] Additional opportunities for incorporating artificial intelligence (AI) into the development and use of digital twins may be explored in the future.

Incorporating AI into MIDD Tools

Incorporating AI into MIDD holds promise to support more streamlined dosing decisions while incorporating timeline efficiency. The biggest near-term impact will be accelerating conventional modelling approaches by automating components of modeling and simulation tasks. Expedition of current processes and scale-up of volume are key impact points. AI-enabled tools may increasingly support more efficient execution of pre-specified modeling workflows, including code generation, model diagnostics, scenario exploration, and documentation, with expert review remaining essential for model specification, quality control (QC), interpretation, and decision-making. AI may also generate or extract more granular and comprehensive clinical data for quantitative modeling; for example, AI-derived lesion-level tumor measurements improved the precision and robustness of TGI models and their association with PFS compared with traditional RECIST-based measurements.[19]

Integrating machine learning (ML) into traditional MIDD methods enables continuous learning. ML approaches may identify complex or nonlinear relationships among exposure, biology, efficacy, toxicity, and patient characteristics. AI/ML can help discover hidden covariates that correlate with efficacy or safety outcomes in non-linear fashion or parameters that do not follow Gaussian distributions. They can also more effectively integrate bioinformatic approaches for large datasets (e.g., proteomics, flow cytometry) with traditional multivariate covariate identification methods to identify covariates for PK or safety/efficacy endpoints. Their value for dosage decisions will depend on interpretability, data quality, external validation, prospective performance, and their ability to quantify uncertainty.

AI may provide an additional tool for cross-checking and integrating information generated across modeling approaches to help inform decisions. With AI, tools could explore a much wider range of combinatorial scenarios and prioritize the best scenarios according to specified criteria. Additionally, AI tools might support multidirectional dose exploration (e.g., exploring dosage levels, step-up-down, patient-stratified

approaches) rather than just moving forward linearly. ML-derived counterfactual prediction can evaluate alternative scenarios as part of pressure testing assumptions of models or dosing decisions.

Conclusions

MIDD has the potential to strengthen and streamline oncology dosage optimization by integrating diverse sources of evidence, quantifying uncertainty, and helping address dosing questions that may be difficult to resolve through clinical evaluation alone. As demonstrated in this framework, the appropriate use of MIDD depends on clearly defining the question of interest, selecting fit-for-purpose modeling approaches, evaluating model credibility and the consequences of model-informed decisions, and interpreting MIDD findings within the totality of available evidence. MIDD evidence should generally complement clinical evidence. The extent of observed clinical data required depends on the context of use, model credibility, residual uncertainty, and consequences of an incorrect decision.

Greater clarity regarding the role of MIDD could enable sponsors to plan more efficient dosage optimization strategies and reduce unnecessary clinical evaluation while maintaining confidence in the selected registrational dosage. This is particularly relevant as oncology development increasingly involves complex dosing regimens, combination therapies, changing disease settings, and patient populations for which traditional clinical dose-finding approaches may be challenging. Emerging approaches, including the incorporation of PROs, RWD, MBMA, digital twins, and AI/ML, may further expand the ability of MIDD to integrate evidence and inform dosing decisions.

Next Steps

Continued collaboration among regulators, industry, academics, clinicians, and patients will be important to advance the application of MIDD in oncology dosage optimization. Key areas for future work include:

- Generating regulatory experience and case examples demonstrating how different MIDD approaches can support specific dosage optimization questions and the level of evidence needed for different types of dosing decisions. Many of these models are used at the IND stage, where analyses are often not publicly shared. Sponsors should publish results and lessons learned for more consistent use across programs, including sharing experiences from MIDD focused programs such as the FDA-MIDD paired meetings.
- Clarifying expectations for model credibility and evidence generation specific to dosage optimization, including how the evaluation of model reliability, model outcomes, and the broader MIDD evidence should be considered in risk-based decision-making for dosage.
- Establishing best practices for integrating MIDD with clinical evidence for challenging dosage decisions, including approaches for characterizing residual uncertainty and determining when additional clinical data are needed.
- Evaluating emerging data sources and methodologies (e.g., PROs, RWD, AI/ML) to determine where these approaches can provide meaningful additional information for dosage decisions.

Collectively, these efforts can help establish a more consistent, transparent, and risk-based approach to incorporating MIDD into oncology dosage optimization and support the selection of dosages that provide the most favorable benefit-risk profile for patients.

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Glossary

Digital twin: A personalized, virtual replica of a real-world patient that integrates individual biological, genetic, and physiological data. Within the framework of MIDD, digital twins leverage computational methodologies such as PBPK and QSP modeling to simulate how specific individuals will absorb, metabolize, and respond to a therapeutic agent. By enabling in silico testing of various dosing regimens, schedules, and escalations across virtual patient cohorts, digital twins optimize early-phase clinical trial designs by predicting individual drug exposure and maximize therapeutic efficacy while minimizing potential toxicities

Disease progression modeling (DPM): A mathematical and statistical framework used to quantify the natural trajectory of a disease over time and predict how different dosing regimens alter that trajectory. By integrating PK/PD data, DPM shifts dose selection from traditional, empirical pairwise testing to continuous, exposure-response optimization

Dosage:[1] The dose and schedule (i.e., the recommended interval between doses and duration of treatment). Can also consider the cumulative exposure to the drug.

Dosage for registrational trials: Decisions about the dose, dosing interval, schedule, duration, and dose-modification strategy for use in the registrational population (i.e., Recommended Phase 2 or 3 Dose (RP2D or RP3D)).

Dose:[1] The quantity of the drug.

Exposure-response (E-R): Considers both the exposure (i.e., the dose and various measures to assess drug concentrations in the body) and response (i.e., the direct measure of the pharmacological effect of the drug).

Model-based meta-analysis (MBMA): A quantitative statistical technique that pools internal clinical trial data with external published or reference data. It goes beyond traditional meta-analysis by utilizing mathematical models to integrate the influences of dose, time, and patient characteristics. In dose finding and dosage optimization, MBMA can analyze historic dose-response relationships and treatment outcomes across various drugs and patient populations

Model informed drug development (MIDD):[5] The use of computational modeling and simulation methods that can include and integrate nonclinical data, clinical data, prior information, and knowledge (e.g., drug and disease characteristics) to generate evidence.

Physiologically Based Pharmacokinetic (PBPK) modelling:[20] A PBPK analysis uses models and simulations that combine physiology, population, and drug characteristics to mechanistically describe the PK and/or PD behaviors of a drug.

Population pharmacokinetics (PopPK):[21,22] PopPK analysis is a well-established, quantitative method that can explain some of the variability in drug concentrations among individuals arising from intrinsic and extrinsic factors along with differences in dosing and routes of administration.

Quantitative systems pharmacology (QSP):[23] An approach that uses mathematical models, disease characteristics, and the dynamic interactions between a drug and biological systems to predict drug activity in compartments (central as well as tissues) of interest to determine an appropriate dose. This is one of the most robust approaches for being able to combine data from *in vitro* and *in vivo* nonclinical experimental systems with clinical trials.

Tumor growth inhibition- overall survival/ progression free survival (TGI-OS/PFS) modeling: An analysis that uses mathematical models to characterize changes in tumor burden over time and quantify the relationship between tumor response and overall survival. By linking early tumor dynamics to long-term clinical outcomes, the approach can help assess treatment benefit, support decision-making, and inform predictions of survival outcomes.

Appendix Table. MIDD tools, the data they incorporate, and the information generated.

MIDD Tool	Data Incorporated into the Model	Information Generated	Dosage Optimization Examples
E-R analyses *Exposure-response analyses* E-R	• Exposure (typically from popPK) • Biomarkers • Efficacy endpoints • Safety endpoints or events • Baseline and time-dependent patient covariates	Exposure response relationship with: • Biomarkers • Safety • Efficacy	• E-R analyses for mosunetuzumab[24]
PopPK *Population pharmacokinetics* Pop PK	• Drug concentration • Dosing history • Patient and baseline characteristics	Exposure data: • Individual and population PK parameters • Between subject variability • Covariate effects	• PopPK for tuvesertib[25]
Longitudinal PK/PD models for safety and efficacy Long PK/PD	• Time course of drug PK • Time course of PD/biomarker measurements • Time course of lab measurements associated with safety or efficacy endpoints	• Relationship between drug concentration and downstream effects as a function of time	• Pop PK/PD modeling for CPX-351[26] • Pop PK/PD modeling for pembrolizumab[27]
TGI-OS/PFS modeling, DPM *Tumor growth inhibition-overall survival/ progression free survival modeling* *Disease progression modeling* TGI-OS DPM	• Longitudinal tumor size measurements • Exposure metrics (from popPK) • Patient characteristics • Time to progression or time to death	• Relationship between drug exposure and tumor size as a function of time • Subsequent relationship between tumor regression and PFS or OS	• TGI-OS in Atezolizumab[28] • TGI-OS in GEMSTONE-302[29] • TGI in Dato-DXd[30,31]

MIDD Tool	Data Incorporated into the Model	Information Generated	Dosage Optimization Examples
TTE *Time-to-event models* 	• Recurrent symptomatic AEs • Dose interruptions and/ or reductions • PROs • Treatment discontinuation	• Time to dose adjustment (reduction or interruption) by exposures • Time to treatment discontinuation by exposures • Time to progression by exposures	• Longitudinal E-R in Belzutifan[32]
QSP *Quantitative systems pharmacology* 	• Biological (pathophysiology, 'omics data, spatiotemporal parameters) • Pharmacological (PK, MoA, *in vitro* and *in vivo* data) • Clinical and population data (e.g., trial results, patient characteristics, literature findings)	• Predicted impact of target modulation, pathway interactions, and combination strategies • Patient selection criteria • Trial enrichment guidance	• QSP in elranatamab[33] • QSP in T-cell bispecifics (mosunetuzumab and blinatumomab)[34]
PBPK modeling *Physiologically Based Pharmacokinetic modeling* 	• Organ and tissue volumes • Blood flow rates • Patient characteristics • Physiochemical and molecular data (i.e., drug parameters) • Biochemical and ADME data (e.g., plasma/tissue bindings, metabolism & clearance, transporter kinetics, route of administration)	• Predicted concentration-time profiles in plasma and relevant tissues • Predicted drug-drug interaction, food-effect, organ impairment, or special-population effects	• PBPK modeling in pembrolizumab[35] • PBPK modeling in abemaciclib on DDI prediction[36]
MBMA	• Efficacy/safety endpoints	• Competitive efficacy benchmarks	• MBMA in PD-1 inhibitors[36–38]

MIDD Tool	Data Incorporated into the Model	Information Generated	Dosage Optimization Examples
Model-based meta-analysis 	• Covariates across the molecules and studies	• E-R relationships • Placebo and standard of care response • Probability of technical success to inform target product profile	

MIDD, Model Informed Drug Development; ADA, anti-drug antibodies; PK, pharmacokinetics; PD, pharmacodynamics; TGI, tumor growth inhibition; AE, adverse event; MoA, mechanism of action; ORR, objective response rate; ADME, absorption, distribution, metabolism, and excretion; PROs, patient reported outcomes