



Review Article

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Evidence Mapping of Model-Informed Drug Development Across Regulatory and Clinical Decisions

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ABSTRACT

Model-informed drug development (MIDD) now supports decisions spanning regulatory interaction, dose selection, population extrapolation, exposure–response assessment, trial design, formulation bridging, and individualized dosing. Yet evidence is often organized by modeling technique rather than by the decision a model is intended to support. This can obscure differences in validation requirements, population transportability, measurement dependence, and acceptable inferential strength. To map contemporary MIDD evidence across regulatory and clinical decision contexts and determine how model class, evidence maturity, transferability, and decision consequence jointly constrain interpretation. An evidence-mapping review was conducted across literature published from 2017 through 2026. Four reproducible PubMed search packages identified 67 records. Nine duplicates were removed, leaving 58 unique records for title/abstract screening. Twenty-two were excluded, 36 proceeded to detailed eligibility assessment, and six were excluded at that stage, yielding 30 eligible evidence units. Evidence was coded by decision context, model type, evidence class, population or product boundary, validation status, and the decision the model was used to inform. The mapped literature showed that identical model classes can occupy materially different evidentiary states depending on the question being addressed. Regulatory programs increasingly use MIDD within structured interactions, but jurisdictional and procedural expectations remain context dependent. Model qualification was particularly sensitive to intended use, external performance, structural-model uncertainty, and transfer to new populations or data environments. Early-development examples demonstrated integration of pharmacokinetic, pharmacodynamic, efficacy, and safety information for dose selection, whereas special-population applications required explicit assessment of physiological and exposure–response comparability rather than automatic extrapolation. MIDD evidence is more usefully interpreted as a decision-conditioned landscape than as a hierarchy of modeling technologies. The proposed mapping separates model identity from evidentiary adequacy and treats validation, transferability, measurement integrity, and reassessment as distinct requirements whose importance changes with the clinical or regulatory consequence of the decision.

Keywords: Model-informed drug development, Pharmacometrics, Population pharmacokinetics, Exposure–response, Physiologically based pharmacokinetics, Precision dosing

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INTRODUCTION

Model-informed drug development encompasses quantitative approaches used to integrate existing knowledge and emerging data in support of drug-development decisions. Regulatory experience in the United States has demonstrated that MIDD can address questions involving dose optimization, trial design, efficacy interpretation, safety, and other development decisions rather than serving as a single modeling methodology [1]. This breadth creates a classification problem: two analyses labeled “MIDD” may differ fundamentally in what they predict, how directly they are validated, and what consequence follows if their assumptions are wrong.

The development of the US Food and Drug Administration paired-meeting pilot provided a structured setting in which sponsors and regulators could discuss model assumptions and decision questions before relying on the resulting analysis [2]. Its subsequent evolution from a pilot into a continuing MIDD meeting pathway reflects institutional maturation of model-focused regulatory interaction [3]. That progression, however, should not be interpreted as evidence that all model outputs have acquired equivalent regulatory status. The evidentiary burden remains inseparable from intended use.

This review therefore maps MIDD evidence by the decision being informed rather than treating modeling technologies as interchangeable categories. We distinguish model representation from validation, validation from population transfer, exposure prediction from response inference, and model-assisted decision support from proof that a proposed biological or clinical mechanism is correct. The central synthesis advanced here is a proposed decision-conditioned evidence map in which evidentiary adequacy depends jointly on model type, available observations, transfer boundary, uncertainty, and the consequence attached to the decision.

MATERIALS AND METHODS

This evidence-mapping review used the search, screening, eligibility, and coding procedures established before manuscript drafting. The review was designed to characterize how quantitative models were used across regulatory and clinical decisions rather than to estimate a pooled treatment effect. Accordingly, evidence units included methodological, regulatory, computational, development-program, and clinical pharmacology publications when they contained a sufficiently specific model-related decision, qualification principle, transfer problem, or implementation boundary.

Four reproducible PubMed search packages were executed on 1 September 2026. Bibliographic and DOI information was independently checked during eligibility assessment, and source journals were required to satisfy the prespecified peer-review, publication-date, and journal-quality criteria. Records were deduplicated by title and DOI before screening. Study characteristics were coded only when directly reported; missing details were not inferred. No meta-analysis, pooled effect estimate, formal certainty grade, or retrospective numerical scoring system was introduced.

Scope and evidence questions

International discussion increasingly frames MIDD as a decision-support discipline requiring clearer and more harmonized expectations for model construction, documentation, evaluation, and regulatory interpretation [4]. Industry experience with formal FDA MIDD interactions likewise emphasizes that the question of interest, available data, modeling strategy, and proposed use must be defined before model output can be interpreted productively [5]. Regulatory progress therefore reflects increasing integration of quantitative analysis into development rather than conversion of modeling into an independent evidentiary endpoint [6]. This distinction also matters geographically: longitudinal evidence from innovative-drug approvals in China indicates increasing MIDD implementation after national guidance, but the pattern is specific to a regulatory system and historical period rather than evidence of identical global uptake [7].

The review addressed four linked questions. First, which model types are being used for which development, regulatory, or clinical decisions? Second, what evidence qualifies a model for the intended question? Third, where does a change in population, physiology, product, assay, dose, or decision horizon create a transfer boundary? Fourth, when should new information trigger reassessment rather than automatic continuation of an earlier model-based decision?

Population transfer was treated explicitly because physiology and data availability can alter the evidentiary meaning of otherwise similar modeling approaches. Pediatric, pregnancy, and geriatric drug development involves distinct developmental, anatomical, physiological, and temporal changes that can alter pharmacokinetics and sometimes pharmacodynamic interpretation [8]. Rare-disease development creates another boundary: quantitative

approaches can integrate limited observations and prior information, but modeling does not eliminate uncertainty generated by small, heterogeneous, or incompletely characterized populations [9].

Search strategy

The search ontology crossed two dimensions. The first captured modeling terminology, including MIDD, pharmacometrics, population pharmacokinetics, physiologically based pharmacokinetics, exposure–response modeling, Bayesian updating, therapeutic drug monitoring, and precision dosing. The second captured the decision context, including regulatory interaction, first-in-human development, dose selection, special populations, trial design, extrapolation, bridging, and individualized dosing.

Eligibility criteria

Eligible evidence units were peer-reviewed journal articles published from 2017 through 2026 that addressed an identifiable MIDD decision, methodological requirement, validation problem, population or product transfer question, or model-informed clinical implementation problem. Regulatory analyses, methodological studies, reviews, development case studies, population-model investigations, PBPK applications, exposure–response analyses, and MIPD studies were eligible when their evidence could be mapped to a specific manuscript claim. Records were excluded when they were merely topically adjacent, failed the publication-window or journal criteria, lacked a completed evidence contribution, or provided commentary insufficient for an indispensable mapped claim. Protocol-only publications were not treated as completed evidence. Model outputs were not classified as mechanistic proof unless the source directly established the relevant mechanism, and formulation or population extrapolation was not equated with demonstrated clinical equivalence.

Decision-context coding

The primary coding unit was the decision state, not the software platform or modeling label. Regulatory–interaction evidence was distinguished from dose-selection evidence; dose-selection evidence was distinguished from population extrapolation; and development decisions were separated from patient-level dose individualization. This prevented a model accepted as informative for one question from being implicitly promoted to a stronger use elsewhere.

Each evidence unit was coded for the question being answered, model class, observed information available at the time of the decision, principal uncertainty, level of external qualification, population or product boundary, and the consequence of acting on the result. A further coding field captured whether later data could plausibly alter the original decision. This reassessment field is part of the review's proposed synthesis, not a previously validated universal MIDD classification.

Model-type classification

Model type remains important, but it was not treated as a proxy for evidentiary strength. For PBPK models, for example, agreement between predicted and observed values may be insufficient when uncertainty around the predictive performance materially changes whether the model is adequate for its intended clinical use. Confidence-aware evaluation has been proposed as a more informative way to characterize predictive performance than reliance on isolated point agreement [10]. Model qualification therefore depends on what error is tolerable for the question being asked, not merely whether the model belongs to a mechanistic category. Population PK models create a different problem when several plausible published models are available. External therapeutic-drug-monitoring data have been used to select or ensemble candidate models for a priori dosing, with performance differing between vancomycin and imatinib settings and among the available model libraries [11]. Patient-specific model selection or averaging has similarly improved vancomycin prediction in a dedicated case study, illustrating that structural-model uncertainty can itself become part of the dosing problem [12]. Tacrolimus provides an implementation-level example: a systematic review and software benchmark identified substantial heterogeneity across population PK models, covariates, and available dosing tools [13]. Consequently, “population PK model available” is not a sufficient evidence state for clinical transfer.

The distinction is summarized in **Table 1**. Its purpose is not to rank model classes, but to show why identical model labels can authorize different actions depending on the clinical state, available evidence, and unresolved uncertainty.

Table 1. Model-class evidence states that determine permissible use in model-informed decisions

Evidence and limits	Permitted action	
Clinical and information state / Dominant PK/PD information / Unresolved uncertainty	Model-derived decision state / Permissible MIDD use	Observation triggering reassessment
Clinical and information state: Physiological representation available; direct evidence in intended population limited Dominant PK/PD information: System parameters, drug-specific properties, simulated exposure Unresolved uncertainty: Structural adequacy, parameter uncertainty, unrepresented physiology	Model-derived decision state: Mechanistic prediction before independent target-population data Permissible MIDD use: Scenario exploration and prediction conditional on model qualification	Systematic discrepancy between predicted and observed target-population PK
Clinical and information state: Independent observations permit performance evaluation Dominant PK/PD information: Predicted and observed concentration or exposure distributions Unresolved uncertainty: Precision of predictive performance and acceptability for the intended consequence	Model-derived decision state: External observations available for a predefined prediction question Permissible MIDD use: Fit-for-purpose support when uncertainty remains within decision-relevant bounds	Confidence around performance crosses the decision-relevant tolerance
Clinical and information state: Candidate models differ in structure, covariates, or source population Dominant PK/PD information: Published population parameters plus external or local PK observations Unresolved uncertainty: Which model or combination transfers best to the current setting	Model-derived decision state: Several plausible population PK models available Permissible MIDD use: Model selection, ensembling, or weighted prediction when discrimination is supported	New observations alter relative predictive performance
Clinical and information state: Individual concentration or response observations accumulate during treatment Dominant PK/PD information: Population prior plus individual observations Unresolved uncertainty: Structural mismatch versus true patient-specific deviation	Model-derived decision state: Patient-specific updating becomes possible Permissible MIDD use: Bayesian updating or individualized forecasting	Persistent prediction error despite additional patient information
Clinical and information state: Model, software, assay, and workflow jointly determine the delivered recommendation Dominant PK/PD information: Calculated exposure and dose recommendation Unresolved uncertainty: Tool implementation, input compatibility, assay-model alignment	Model-derived decision state: Model implemented through a dosing tool Permissible MIDD use: Clinical decision support after local qualification	Recommendation changes materially with model, software, or measurement platform

Evidence mapping

The evidence map was constructed across four intersecting dimensions: decision context, model representation, evidence state, and transfer boundary. This structure avoids a common interpretive shortcut in which increasing model complexity is assumed to correspond to increasing decision credibility. A simple empirical exposure–response model may be highly informative for a tightly defined dose question, while a mechanistically rich model may remain insufficient for a population-transfer decision if its external validity is uncertain.

Evidence maturity was also treated as dynamic. A model may begin as a mechanism-supported prior, acquire internal clinical observations, undergo external evaluation, and then encounter a new population or implementation environment that reopens uncertainty. The evidence state therefore does not advance irreversibly. At each transition, the admissible inference depends on whether the new information tests the same quantity and context that the decision requires.

Program-level evidence reinforces the importance of separating model use from model identity. Portfolio analyses have estimated reductions in development time or trial cost associated with MIDD-supported activities, but such estimates are dependent on the company, programs, assumptions, and counterfactual development pathways

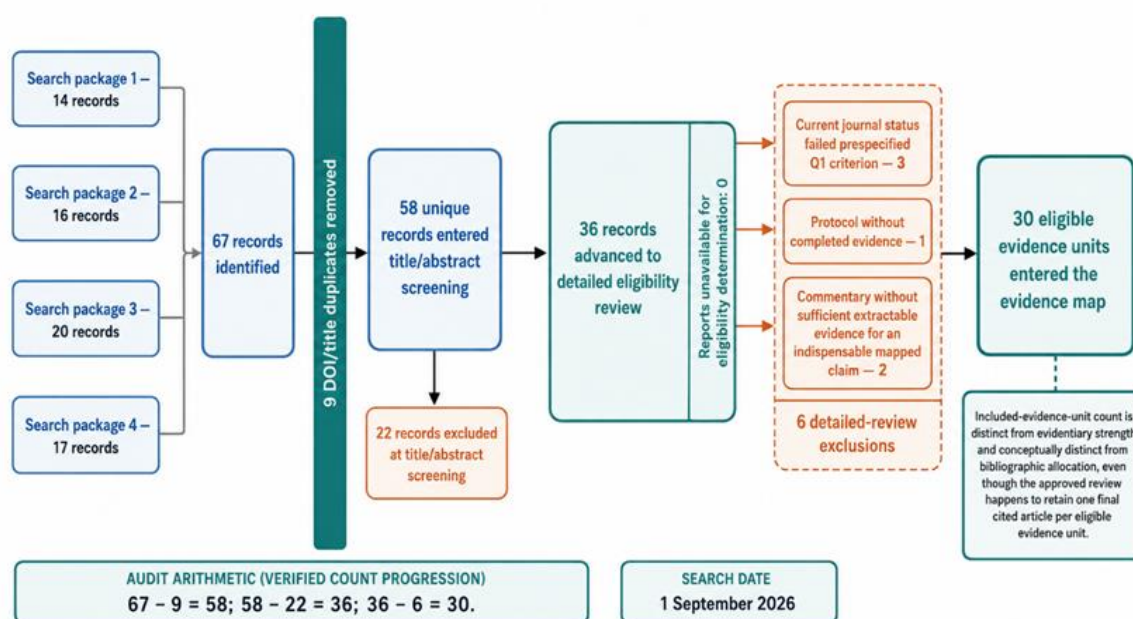
studied [14]. They provide evidence that MIDD can influence development efficiency, not a causal estimate that any model will shorten any future development program.

Table 2 converts this logic into evidence states. Unlike **Table 1**, which focuses on uncertainty among model representations, **Table 2** follows how the evidentiary meaning of an exposure or response prediction changes as observations accumulate or the decision context changes.

Table 2. Evidence-state transitions that condition interpretation across model-informed drug development

State and entry conditions	Evidence through time	Transition and reassessment
State-changing observation	Governing evidence state / Exposure representation available / Response or target information available	Decision endpoint that can be supported / Boundary unresolved
First informative observations in the decision population	Governing evidence state: Prior-informed prediction Exposure representation available: Simulated or prior-informed exposure Response or target information available: Mechanistic, preclinical, or limited clinical response information	Decision endpoint that can be supported: Scenario prioritization and design of the next evidence-generating step Boundary that remains unresolved: Human or intended-population transfer
Independent dataset or materially different trial population	Governing evidence state: Internally calibrated development model Exposure representation available: Clinical PK informs parameter estimation Response or target information available: Trial-specific PD, efficacy, safety, or biomarker observations may be available	Decision endpoint that can be supported: Dose or trial decisions within the studied development context Boundary that remains unresolved: External validity and unstudied covariate space
Evidence from the new intended-use setting	Governing evidence state: Externally challenged prediction Exposure representation available: Prediction is evaluated against independent observations Response or target information available: Response confirmation may remain endpoint-specific	Decision endpoint that can be supported: Stronger support for the prespecified question of interest Boundary that remains unresolved: Transfer to a new population, product, assay, or decision horizon
Discordant PK, PD, safety, or clinical outcome pattern	Governing evidence state: Cross-population or cross-product transfer Exposure representation available: Exposure similarity or mechanistic prediction may be estimable Response or target information available: Response similarity may be incomplete or assumed	Decision endpoint that can be supported: Conditional extrapolation or targeted additional evidence generation Boundary that remains unresolved: Whether exposure equivalence implies response equivalence
Persistent residual error, changed covariate state, or conflicting response	Governing evidence state: Decision implemented with ongoing data Exposure representation available: Model prediction is connected to trial or patient observations Response or target information available: Longitudinal response may modify the interpretation	Decision endpoint that can be supported: Adaptive development or individualized reassessment Boundary that remains unresolved: Model drift, measurement compatibility, evolving physiology

The review-selection arithmetic underlying this evidence map must remain distinct from the scientific strength of individual evidence units. **Figure 1** therefore shows the verified identification and screening pathway while preserving the four search-package contributions and the separation between included evidence units and the final interpretive map.

**Figure 1.** Source-resolved selection architecture for the decision-context MIDD evidence map

RESULTS AND DISCUSSION

The verified search identified 67 records before deduplication. Removal of nine duplicates left 58 unique records; 22 were excluded at title/abstract screening, and 36 proceeded to detailed eligibility assessment. Six additional exclusions yielded 30 eligible evidence units. The resulting map covered regulatory implementation, model qualification, special-population transfer, development efficiency, first-in-human and subsequent dose selection, exposure–response decision support, trial adaptation, formulation bridging, and model-informed clinical dosing. The mapped evidence did not support a universal ranking of model classes. Instead, model adequacy was repeatedly conditional on the question of interest and the data environment in which the prediction would be used. Evidence relevant to regulatory communication was not equivalent to evidence establishing transportability to an unstudied population; likewise, internal predictive performance did not remove the need for external qualification when a model moved toward direct clinical use.

A second recurring pattern was the presence of re-entry into uncertainty. New population data, discrepant measurements, alternative model structures, or a change in the decision itself could return an apparently mature model to a lower-confidence evidentiary state. This finding underpins the review's proposed use of reassessment triggers rather than representing MIDD as a one-directional progression from model construction to acceptance.

First-in-human and dose selection

First-in-human dose selection illustrates why decision context should precede model classification. Starting-dose methodologies are designed primarily to control uncertainty at the transition from nonclinical evidence to human exposure. Risk-based recommendations emphasize integration of pharmacology, toxicology, anticipated human pharmacokinetics, biological activity, modality-specific hazards, and uncertainty rather than reliance on one universal conversion rule [15]. A model used here is therefore evaluated partly by whether its assumptions are conservative and transparent enough for the initial human-risk question, not by whether it maximizes prediction precision across later development.

Dose selection after human data accumulate is a different evidentiary state. In a phase I study of the PRMT5 inhibitor PF-06939999, PK/PD modeling was used to connect exposure with pharmacodynamic information and tolerability to inform an expansion-dose decision [16]. The example demonstrates a shift from minimizing uncertainty before first exposure to balancing observed human pharmacology and safety across candidate doses. It does not establish that model selection itself proves antitumor efficacy.

Datopotamab deruxtecán provides a further distinction. Population PK and exposure–response analyses were updated iteratively during phase I and used to support selection of a late-stage regimen rather than defaulting to the maximum tolerated dose [17]. The evidentiary value arose from the alignment of a specific drug, observed exposure range, efficacy and safety endpoints, and development question. Thus, the same broad label—dose

selection—contains materially different decision states before first human exposure, during dose expansion, and during transition to late-stage development.

These examples support a central rule for the proposed map: model-derived dose recommendations should be interpreted against the decision horizon. An analysis adequate for selecting the next dose cohort need not automatically be adequate for establishing a registrational regimen, and neither use implies that the model has demonstrated the underlying pharmacological mechanism with certainty.

Special populations

Special populations expose the limits of treating exposure prediction as equivalent to clinical extrapolation. FDA experience with pediatric exposure–response analyses shows that such models can support several distinct decisions, including assessment of adult-to-pediatric extrapolation, pediatric dose selection, and evaluation of a new formulation, regimen, or administration route [18]. These uses depend on what is known about similarity in disease, exposure, and response. Pharmacokinetic comparability alone cannot establish pharmacodynamic or clinical-response equivalence when the latter remains uncertain.

The distinction is particularly important because “special population” is not one biological state. Developmental maturation, pregnancy-related physiological changes, aging, body composition, organ function, concomitant therapies, and disease-specific factors may influence parameters at different levels of a model. Accordingly, the relevant transfer question is not simply whether a model predicts concentration, but whether the physiological representation, parameter relationships, endpoint, and uncertainty remain appropriate for the decision in the target population.

Nemolizumab development in moderate-to-severe atopic dermatitis provides a contemporary adult–adolescent example. Integrated MIDD analyses supported clinical development and dosing across the studied age groups [19]. The case is informative because it demonstrates that cross-age development can be supported quantitatively without assuming that all adolescent and adult pharmacological states are interchangeable. Its evidentiary scope remains tied to nemolizumab, atopic dermatitis, the studied exposure range, and the available adult and adolescent data.

In the proposed decision-conditioned evidence map, special-population use therefore introduces a transfer boundary rather than a routine continuation of the source-population model. Crossing that boundary requires explicit consideration of which physiological and pharmacological relationships are expected to remain stable, which are estimated from target-population observations, and which remain assumptions. Where response information is limited, the correct result may be targeted evidence generation rather than stronger extrapolation. This preserves a distinction that becomes increasingly important later in development: successful prediction of exposure can support a decision without proving equivalence of response, benefit–risk, or optimal dose across populations.

Exposure–response decisions

Exposure–response analysis becomes decision-relevant only when exposure, endpoint, time scale, and population correspond to the question being asked. Ligelizumab development illustrates this principle: pharmacometric analyses were linked to concrete clinical-development decisions rather than treated as self-sufficient demonstrations of efficacy or mechanism [20]. The important evidentiary unit is therefore not merely an estimated exposure–response relation, but the relation together with its endpoint definition, studied exposure range, covariate structure, uncertainty, and intended decision.

Longitudinal pharmacology makes this distinction more important. Daprodustat development integrated population pharmacokinetics with longitudinal hemoglobin response and simulation to support regimen design in patients with chronic kidney disease [21]. When response evolves after exposure and subsequent dose modification alters future exposure, a static exposure summary can conceal the feedback structure relevant to dosing. The proposed framework therefore treats dose adaptation as a changing decision state rather than a single exposure–response calculation.

Table 3 separates the conditions under which exposure–response information can support different forms of action without turning observed association into mechanistic or causal certainty.

Table 3. Exposure–response decision states under changing pharmacological and clinical information

Decision context	Evidence and limits	Permitted action
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Dose-adaptation state / Temporal structure / Covariate trajectory	Exposure information / Response information	Non-negotiable boundary	Permissible decision consequence
Dose-adaptation state: Initial human dose exploration Temporal structure: Short observation horizon Covariate trajectory: Baseline covariates dominate	Exposure information: Sparse observed exposure plus prior expectations Response information: Early pharmacodynamic or tolerability observations	Early signal does not establish durable benefit–risk	Refine subsequent dose exploration
Dose-adaptation state: Expansion-dose evaluation Temporal structure: Repeated observations across cohorts Covariate trajectory: Important covariates increasingly estimable	Exposure information: Observed PK across candidate doses Response information: Target response, safety, or early efficacy endpoint	Association within studied exposure range should not be extrapolated without support	Compare candidate dose regions
Dose-adaptation state: Late-stage regimen selection Temporal structure: Trial-relevant follow-up Covariate trajectory: Covariate distributions better characterized	Exposure information: Population exposure distribution under candidate regimens Response information: Efficacy and safety endpoints relevant to the intended population	Model support does not substitute for required clinical evidence	Support a registrational regimen hypothesis
Dose-adaptation state: Longitudinal dose adaptation Temporal structure: Explicit lag and feedback Covariate trajectory: Organ function, disease state, or treatment history may change	Exposure information: Updated patient or population exposure Response information: Delayed or repeatedly measured pharmacodynamic response	Historical covariate relationships may become stale	Adapt future dose according to current state
Dose-adaptation state: Individualized reassessment Temporal structure: Sequential updating Covariate trajectory: Covariates may evolve between visits	Exposure information: Patient observations compared with model prediction Response information: Patient-specific response or toxicity information	Persistent model–patient discordance requires reassessment	Continue, modify, or reconsider an individualized recommendation

Trial design

MIDD can also influence the structure of evidence generation itself. In the ZENITH development program, model-informed interpretation contributed to revision of dose strategy as information about efficacy and fluid-retention risk accumulated [22]. This is qualitatively different from using a finalized model to answer a fixed question: the model participates in a feedback process in which emerging observations can alter assumptions, candidate doses, or the next trial decision.

Cross-stage reuse is illustrated by upadacitinib, for which quantitative approaches were applied across multiple development decisions rather than rebuilt as unrelated analyses at each stage [23]. Such reuse can preserve information continuity, but it does not imply that a model qualified for one stage remains automatically qualified when the population, endpoint, formulation, or regulatory question changes.

The proposed architecture therefore treats trial design as a decision boundary between what existing evidence can justify and what the next study must resolve. The model can narrow uncertainty, but unresolved physiology, response heterogeneity, structural assumptions, or population transfer should remain visible rather than being converted into apparently precise design choices.

This boundary is represented in **Figure 2**, which separates physiological variation, quantitative prediction, trial observation, and dose decisions while preserving feedback when new evidence contradicts the model.

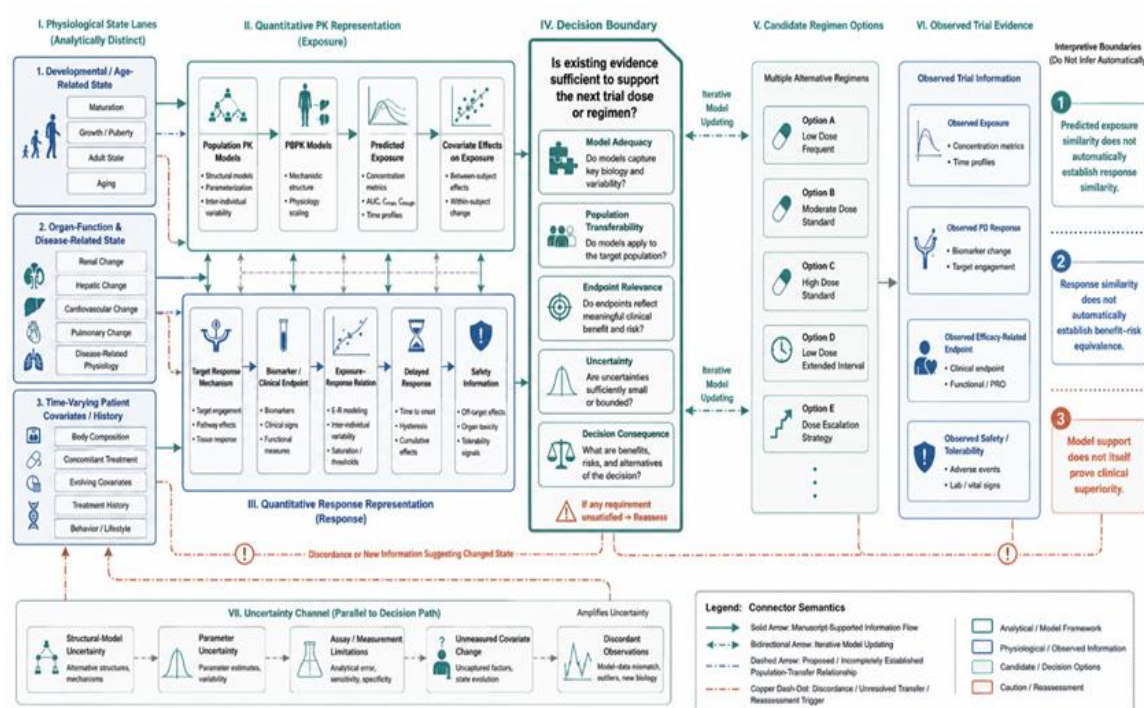


Figure 2. Trial-design boundary linking special-population physiology, quantitative prediction, and dose reassessment

Regulatory waivers and extrapolation

Model-informed extrapolation becomes particularly demanding when the object being transferred is not a population but a formulation or product state. PBPK modeling of a sustained-release flucytosine formulation illustrates how mechanistic simulation can connect formulation properties with expected systemic exposure and thereby inform formulation-development strategy [24]. The value of such modeling is conditional on whether the physiological representation, release assumptions, and predictive performance are adequate for the formulation question.

The evolving role of in vitro–in vivo correlation and physiologically based biopharmaceutics modeling likewise reflects a shift from descriptive correlation toward decision-oriented prediction [25]. These approaches can support formulation development or regulatory questions, but an in vitro relationship becomes decision-relevant only when its connection to in vivo exposure is sufficiently characterized for the intended use.

Talazoparib provides a more difficult case. Model-informed analyses contributed to formulation bridging despite failure of conventional bioequivalence criteria [26]. This example demonstrates that discordant conventional and model-derived evidence can sometimes be resolved through a broader evidentiary assessment. It does not establish a general rule that failed bioequivalence can be overridden by modeling. In the proposed evidence map, such cases occupy a high-scrutiny state in which model validity, formulation mechanism, exposure interpretation, clinical relevance, and regulatory context must remain explicit.

Clinical dose individualization

The evidentiary problem changes again when the decision concerns an individual patient rather than a development population. In antibiotic therapy, the transition from conventional therapeutic drug monitoring to MIPD has been framed around combining population models, patient observations, and Bayesian updating to forecast individualized exposure and future dose requirements [27]. This allows concentration measurements to update a quantitative prior rather than functioning only as values compared with a fixed therapeutic interval. Contemporary MIPD literature nonetheless emphasizes that model availability is not equivalent to clinical implementation readiness [28]. Data quality, appropriate sampling, model qualification, computational integration, clinician workflow, and prospective assessment can each become limiting steps. Outcome improvement should therefore be treated as an empirical question rather than as an automatic consequence of personalization.

External model evaluation is a distinct requirement. Guidance on the selection of population PK models for precision dosing emphasizes that a published model should be tested against independent data and against its

intended clinical purpose before use in a new population [29]. A model can fit its development dataset well and still be poorly transportable because covariate distributions, clinical practices, assay platforms, or disease characteristics differ.

Measurement compatibility adds another layer. In ustekinumab treatment for Crohn's disease, assay-dependent concentration differences were shown to propagate into model-informed interpretation and dosing recommendations [30]. Thus, a clinically implemented MIPD system is not only a model: it is a chain connecting specimen, assay, observation, model, patient state, and dose decision.

Table 4 separates these competing failure explanations so that persistent prediction error is not automatically assigned to the patient, the model, or the assay without discrimination.

Table 4. Discriminating sources of discordance in clinical model-informed dose individualization

Observed configuration	Mechanism and competing diagnosis	Corrective discrimination
Clinical dosing scenario / What is directly observed / What is inferred	Competing explanation	Observation that discriminates the explanations / Consequence for dose decision
Clinical dosing scenario: Concentration differs from model prediction What is directly observed: Measured drug concentration What is inferred: Individual clearance or distribution differs from prior expectation	Model structural mismatch, changing physiology, sampling error, or assay effect	Observation that discriminates the explanations: Repeat measurement, timing verification, external-model check, covariate reassessment Consequence for dose decision: Avoid immediate dose escalation until source of discordance is clarified
Clinical dosing scenario: Predictions remain biased after Bayesian updating What is directly observed: Sequential concentrations and doses What is inferred: Patient-specific parameters remain inadequately represented	Incorrect model structure or omitted time-varying covariate	Observation that discriminates the explanations: Persistent residual pattern despite informative new observations Consequence for dose decision: Reconsider model choice rather than indefinitely updating the same structure
Clinical dosing scenario: Published model performs poorly locally What is directly observed: External-population predictions versus observations What is inferred: Original covariate relationships do not transport	Population difference, clinical-practice difference, or incompatible measurement process	Observation that discriminates the explanations: Independent local validation and covariate diagnostics Consequence for dose decision: Select, recalibrate, ensemble, or reject candidate model
Clinical dosing scenario: Different assays produce meaningfully different concentrations What is directly observed: Assay-specific concentration measurements What is inferred: Exposure and future dose differ according to assay input	Analytical non-equivalence rather than biological change	Observation that discriminates the explanations: Cross-assay comparison under matched samples Consequence for dose decision: Match assay to model or revalidate the model–assay combination
Clinical dosing scenario: Clinical response conflicts with apparently adequate exposure What is directly observed: Concentration and clinical response What is inferred: Exposure target is assumed to represent desired response	Pharmacodynamic heterogeneity, disease change, tolerance, delayed response, or endpoint mismatch	Observation that discriminates the explanations: Longitudinal response assessment and alternative PD explanation Consequence for dose decision: Do not increase dose solely to reproduce a population exposure target

Evidence gaps

The map identifies four recurrent gaps. First, prospective demonstration that a model-informed decision improves a clinically meaningful outcome remains uneven across applications. Second, external validity is often tested less thoroughly than internal predictive performance, particularly when published models move into new populations or software environments. Third, measurement integrity—including assay compatibility and timing

of clinical observations—can be treated as peripheral even though it directly conditions model input. Fourth, time-varying physiology and response can invalidate covariate relations that appeared adequate earlier in treatment.

These gaps imply a validation agenda focused less on producing additional model variants and more on testing decision robustness. Priority questions include whether conclusions persist under plausible alternative structures, whether external populations reproduce relevant predictive behavior, whether measurement systems are compatible with model assumptions, and whether predefined reassessment triggers detect model–patient or model–trial discordance before it becomes clinically consequential.

The mapped evidence supports MIDD as a family of decision-support practices rather than a uniform evidentiary technology. Regulatory analyses, development case studies, PBPK investigations, population-model evaluations, exposure–response studies, and MIPD applications repeatedly show that the same broad methodology can serve different purposes. The critical interpretive question is therefore not “Was a model used?” but “What decision was the model qualified to inform?”

This perspective also changes how model sophistication should be interpreted. Mechanistic complexity can be valuable when the decision depends on physiological extrapolation, while a simpler empirical model may be more adequate for a narrowly observed exposure–response question. Conversely, mechanistic detail does not compensate for weak external validation, incompatible measurements, or a poorly specified clinical question.

A second synthesis is that evidence maturity is reversible. Trial observations can contradict prior predictions; new populations can reopen transportability questions; changing organ function can invalidate earlier covariate assumptions; and assay differences can alter the observations on which an individualized recommendation depends. The proposed decision-conditioned map therefore includes explicit reassessment routes rather than a one-way progression from construction to validation to application.

No mapped source establishes a universal model hierarchy or a universal clinical benefit from MIDD. The strongest defensible conclusion is narrower: quantitative models can materially inform decisions when the model, evidence, population, measurement system, uncertainty, and decision consequence are aligned. Increasing the consequence of a wrong decision increases the importance of demonstrating that alignment.

Decision–model landscape

The principal synthesis of this review is a proposed Decision–Model Landscape with four independent coordinates.

The first coordinate is decision consequence: exploratory simulation, development optimization, regulatory bridging, trial-dose choice, or patient-specific dosing carry different tolerance for prediction error. The second is model representation, encompassing empirical exposure–response, population PK, PK/PD, PBPK, Bayesian updating, and related approaches without assigning them a universal rank. The third is evidence state, ranging from prior-informed prediction through internal calibration and external challenge to repeated observation during implementation. The fourth is transfer boundary, including new physiology, population, formulation, assay, disease state, or decision horizon.

A model-supported action is strongest when these coordinates are explicitly aligned. Discordance in any coordinate should trigger reassessment at the level where the mismatch originates. A poor clinical prediction need not imply that every component of the model is wrong; likewise, accurate exposure prediction does not establish response equivalence if the response model remains untested.

This landscape reframes MIDD evaluation from asking whether a model is “validated” in the abstract to asking whether the evidence is adequate for a specific consequence under a specific set of boundaries. It also preserves a practical distinction between evidence-supported use and proposed extension. The former remains within the population, product, measurement system, exposure range, and endpoint supported by data; the latter crosses one or more boundaries and therefore requires explicit justification or additional evidence.

CONCLUSION

Evidence across regulatory and clinical MIDD applications is heterogeneous because the decisions themselves are heterogeneous. Model identity does not determine evidentiary strength independently of intended use, external validity, population or product transfer, measurement compatibility, and the consequence of error.

The proposed Decision–Model Landscape organizes these requirements without treating increasingly complex modeling as progressively stronger evidence. It instead positions modeling as a conditional component of an

evidence chain. MIDD is most defensible when uncertainty remains visible, transfer is tested rather than presumed, discordant observations can reopen earlier assumptions, and the model-supported decision is no stronger than the evidence state permits.

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