Quantitative Systems Pharmacology (QSP)-Based Dose Selection for Minimum Anticipated Biological Effect Level (MABEL) in First-in-Human (FIH) Trials

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Office of Clinical Pharmacology Guidance and Policy Team at CDER_OCP_GPT@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical Pharmacology

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Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist sponsors[2] by providing the Agency's recommendations on the appropriate use of a quantitative systems pharmacology (QSP)-based approach for determining minimum anticipated biological effect level (MABEL) dose in first-in-human (FIH), phase 1 trials. QSP is an approach that uses mathematical models, disease characteristics, and the dynamic interactions between a drug[3] and biological systems to determine an appropriate FIH dose. This approach has the potential to reduce reliance on animal toxicology studies.
The integration of QSP models in FIH dose selection aligns with the Agency's commitment to model-informed drug development (MIDD), which encourages the use of quantitative modeling and simulation to inform drug development and regulatory decisions.

[1] This guidance has been prepared by the Office of Clinical Pharmacology, Office of Translational Sciences, in collaboration with Pharmacology/Toxicology, Immediate Office, Office of New Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, the term *sponsor* refers to both sponsors and applicants.

[3] For purposes of this guidance, references to *drug* or *drugs* includes drugs approved under section 505 of the FD&C Act (21 U.S.C. 355) and biological products licensed under 351(a) of the PHS Act (42 U.S.C. 262(a)) that are regulated as drugs. Hereafter, the term *drug* or *drugs* will be used to refer to all such products unless otherwise specified.

The focus of this guidance is on drugs for which the MABEL approach is recommended to guide starting doses for FIH trials. This can, but does not necessarily, include drugs that cause T-cell activation and subsequent cytokine release. Here, we provide recommendations for leveraging mechanistic QSP as a model-based approach to improve FIH dose estimation.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Selecting an appropriate initial dose for FIH trials is a critical step in drug development. Historically, FIH starting doses were often derived from animal toxicology studies and have been based on the no observed adverse effect level (NOAEL), severely toxic dose in 10% of rodents (STD10), or highest non-severely toxic dose in non-rodent species (HNSTD), converted to a human equivalent dose. Although these approaches have been appropriate for many drugs, there are limitations for certain high-risk products (e.g., immunostimulatory monoclonal antibodies). In response, the concept of MABEL was developed. MABEL is defined as a dose expected to produce a minimal biological effect in humans. Determining MABEL typically involves using pharmacologic activity and receptor binding data (human cell lines), while also integrating any other relevant data, (e.g., pharmacokinetic data), as appropriate, to predict a dose that is just at the onset of biological activity.

Quantitative Medicine approaches can be powerful for data integration and dose selection. Specifically, QSP has emerged as an approach to model disease characteristics and complex drug–biological system interactions. QSP merges an understanding of biological systems and a drug's exposure-response relationship, enabling modeling and simulation of how a drug engages its target and triggers downstream biological responses in a mechanistic, quantitative manner. Over the past decade, there has been a notable increase in regulatory submissions (e.g., investigational new drug applications (INDs), biologics license applications (BLAs), and new drug applications (NDAs)) that used a QSP approach to support various decisions, such as informing FIH dose selection, particularly for drugs where traditional methods may fall short. For example, certain drugs have highly specific targets that only exist in humans and can elicit steep pharmacodynamic responses (e.g., cytokine release or T-cell activation) that are difficult to predict from animal studies alone. In many cases, the relevant target may be absent or differently expressed in animal species, limiting the translational relevance of animal toxicity data, and standard allometric scaling of doses might not account for such pharmacological differences. Therefore, a model-informed approach that considers all available data (e.g., in vitro, in vivo, in silico) could be more appropriate to estimate a starting dose in the FIH trial. In addition, QSP modeling can provide simulated data for both therapeutic effect and safety, which can help enable a quantitative balance to inform FIH dose selection. This guidance specifically outlines

how QSP models can be developed and used to estimate a MABEL dose for drugs entering FIH trials.

III. GENERAL PRINCIPLES OF QSP IN FIH DOSE SELECTION

QSP provides a framework to integrate mechanistic understanding and diverse data into a predictive model. For a MABEL-based FIH dose, the primary goal of the QSP model is to estimate a dose that is expected to result in a minimal but measurable biological effect in humans.

Sponsors should consider several guiding principles for the use of a QSP approach for MABEL dose determination in FIH trials:

- *Integration of All Available Data*: A foundational principle for QSP modeling is to consider all relevant data for dose prediction. This includes in vitro studies (such as the following assays in human cells: target binding affinity, receptor occupancy and activation, and cytokine release), in vivo studies in relevant animal species (e.g., pharmacokinetic and pharmacodynamic studies), ex vivo studies, in silico studies, an understanding of disease biology, and learnings from compounds with both similar structure and similar mechanism of action or compounds that partially share pharmacological pathways.

- *Accounting for Species Differences and Scaling to Humans*: If using animal data in the model, QSP models need to incorporate species-specific data such as physiological parameters, receptor densities, and pharmacodynamic responses. This is necessary for the QSP models to translate nonclinical data to clinical predictions.

- *Mechanistic Representation of the Biological Mechanisms Involved in Drug Response*: In general, QSP models should represent the complete, relevant sequence of events from drug administration, absorption, and distribution to molecular target engagement, activation of signaling pathways, and subsequent biological responses. A model should also take into consideration the expression level of the molecular target and its turnover. By doing so, the model is expected to better predict therapeutic effect and potential adverse reactions as a function of dose.

- *Understanding Model Uncertainties and Iterative Refinement*: A QSP model is a synthesis of the current understanding of biological and pharmacological knowledge, which is likely to evolve with time. As additional data — such as results from new nonclinical studies or early-phase clinical trials — become available, sponsors should consider refining the model. Refining the model is especially crucial when early clinical data contradict model predictions. Integrating emerging data from initial patients allows for real-time updating of model assumptions and parameter values and adaptive decision-making. This aligns with the core principles of MIDD, which emphasize continuous learning and confirming as data accrue. Sponsors should include in their

submission the assumptions used in a model and the assumptions' impact on the FIH dose proposed.

IV. RECOMMENDED QSP MODELING PRACTICES

Consistent with the International Council for Harmonisation (ICH) guidance for industry *M15 General Principles for Model-Informed Drug Development* (June 2026),[4] the recommendations in this section are aimed to ensure the QSP model is sufficiently reliable to determine appropriate doses for FIH trials that are safe but not subtherapeutic. Sponsors should provide the following information in their submission when using QSP for dose selection in FIH trials:

- *Question of Interest*: Sponsors should clearly state the question of interest that will be answered by the model (e.g., the model will be used to determine the starting dose, anticipated target dose range, and/or planned dose-escalation scheme in the FIH trial).

- *Context of Use (COU)*: Sponsors should clearly define the specific role and scope of the QSP model within a given context. In general, sponsors should explain how the model prediction will be used to answer the question(s) of interest and clarify what other information will be used in the model.

- *Model Risk Assessment*: Sponsors should assess model risk based on the following two key factors that will guide the expectation for the model performance and model validation:

  - Model influence (i.e., the intended weight of the model outcomes in decision-making considering the contribution of other relevant information such as dose selection based on another method).

  - Consequence of making a wrong decision (i.e., consequences if a wrong decision is made based on all available information). The mechanism of action and anticipated safety profile of a drug can impact the consequence of making a wrong decision.

- *Model Construction*: During model construction, sponsors should consider the following recommendations:

  - QSP model structure should be built to represent the disease and the biological mechanisms related to the pathways targeted by the drug.

[4] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fdaguidance-documents.

  - Critical components should be identified, including target expression on relevant cells, biomarker turnover dynamics, downstream pathways, protein binding, metabolism or transport, and target tissue or compartment of localization. For some drugs, the model should incorporate multiple biological subsystems to reflect potential pharmacological effects and safety concerns.

  - Model equations and assumptions should be biologically plausible and supported by established scientific knowledge.

  - Acknowledgements should be provided when certain biological processes, such as potential off-target interactions or speculative feedback loops, are not represented within the model due to limited data or uncertainties about their existence.

  - Evaluations should be conducted, if possible, with alternative model structures that incorporate these additional elements to determine whether their inclusion substantially alters model predictions.

- *Parameterization*: Sponsors should obtain model parameters from reliable sources when possible, such as direct experimental measurements.

  - For biological products, it is especially critical to recognize that target interactions and immune responses can differ significantly between species. Thus, if a biological product's therapeutic target is human-specific — as often occurs with monoclonal antibodies — binding parameters should ideally be characterized using human-derived cells or tissues.

  - Animal studies or other nonclinical studies can be used to estimate parameters for drug pharmacokinetics (e.g., clearance, volume of distribution) and pharmacodynamics (e.g., maximal effect observed, tolerance development), when appropriate. However, it is crucial to assess the extent to which each nonclinical model mirrors human biology, particularly regarding drug-target interactions and downstream biological effects. In certain cases, data derived from transgenic animal models expressing human targets can be employed. Sponsors should ensure that species-specific parameters (e.g., target expression, binding affinity) are appropriately chosen for human or nonclinical models. Sometimes, physiological parameters and drug-specific parameters may vary based on different data sources. Biological variability within human participants (e.g., between cancer patients or healthy volunteers) could impact response and should be accounted for in the models.

- *Code Development*: Sponsors should develop the QSP model using reliable computational software and document the code thoroughly.

- *Model Verification*: Sponsors should conduct verification procedures to confirm that the model equations and coding implementations are free of errors, such as incorrect calculations or inconsistent units. Sponsors should verify basic model behaviors during initial checks. For example, sponsors should ensure that the absence of drug administration results in no pharmacological effect and that sufficiently high drug doses lead to target saturation. For stochastic models, sponsors should verify stochastic stability to ensure consistent and realistic variability across simulations.

- *Model Calibration and Validation*: Sponsors should thoroughly document the calibration process, including methods, rationale for parameter adjustments, and the resulting alignment with observed data to ensure transparency. QSP model validation should be driven by the COU and model risk. When feasible, sponsors should evaluate the model prediction against data collected in clinical and nonclinical studies. Model performance can be validated by different components (e.g., biomarker changes in disease progression, and with treatment). Clinical data from drugs with the same mechanism of action or sharing the underlying pharmacological pathways can provide additional assurance of the reliability of the model.

- *Model Application*: After successful validation, the model can be applied to predict the drug responses under different dosing regimens. This can lead to the prediction of the FIH dose and potential suggestions for dose-escalation increments. Specifically, simulating pharmacological responses at multiple low-dose levels surrounding the anticipated starting dose can help visualize the steepness or shallowness of the dose-response relationship. A gradual (shallow) response at low doses can support selection of a slightly higher initial dose, whereas a pronounced (steep) increase in response indicates the importance of a lower starting dose and more cautious subsequent dose escalation.

- *Sensitivity and Uncertainty Analyses*: Sponsors should conduct sensitivity analyses to systematically determine how changes in individual model parameters influence predictions and dosing recommendations. Sponsors should address model structural uncertainty by evaluating alternative biological hypotheses and model architectures. Sponsors should quantify how collective knowledge gaps, both in parameter estimates and underlying biological assumptions or model structures, affect the overall confidence in model predictions. These analyses help identify parameters and/or structure assumptions with the greatest impact on outcomes and evaluate the robustness of dose recommendations across realistic parameter and model structure variations. Sponsors should thoroughly communicate the impact of the model parameters and/or structure assumptions on the robustness of the proposed FIH dose to ensure transparency.

- *Dose Selection*: The selection of a FIH dose relies on multidisciplinary collaboration based on the totality of available data, and sponsors should include the following considerations:

- In general, sponsors should err on the side of caution when selecting the FIH starting dose for the safety of the clinical trial participants. Additional caution is warranted when a QSP-based dose differs substantially from traditional MABEL estimates (those using in vitro pharmacology activity and binding studies conducted with the investigational product). In such cases, sponsors should demonstrate the model's reliability, ideally through retrospective validation using clinical outcomes from compounds with a similar mechanism of action (and structure, as applicable).

- For novel targets lacking clinical precedent, if discordant dose estimates arise between the QSP model and traditional methodologies, sponsors should select the most conservative (lowest) starting dose to prioritize patient safety.

- Sponsors should explicitly incorporate findings from sensitivity and uncertainty analyses to determine the FIH dose and clearly identify how variations in key model parameters and underlying assumptions affect predicted dose-response relationships and confidence in model-based dose recommendations. Additional safety margins could be appropriate, depending on the anticipated severity, reversibility, and clinical manageability of potential adverse effects suggested by the drug's mechanism of action. If the target or mechanism of action of the drug is novel, additional safety margins should also be considered.

- It is worth noting that MABEL, by definition, is a low-end dose. In studies involving patients with life-threatening disease (e.g., some oncology and severely debilitating or life-threatening indications), sponsors should consider avoiding prolonged escalation phases where many patients are exposed to sub-therapeutic dose levels. In some cases, starting at a minimal active dose that is higher than the absolute MABEL may be justified. QSP models can help determine that minimal active dose. This is a nuanced decision and should consider patient safety versus potential benefit. Sponsors should submit appropriate justification for starting at a dose higher than the absolute MABEL.

- *Early Monitoring and Model Refinement*: Sponsors should identify the model's limitations, such as potential information gaps and model uncertainties, and provide the following information:

  - Sensitivity and uncertainty analyses can help, but cannot address, unanticipated biology. Thus, even with a model-predicted safe dose, sponsors should remain vigilant for unexpected reactions and consider safety measures such as staggered enrollment and intensive monitoring in the FIH trial design, especially for certain high-risk drugs.

- Ideally, the FIH trial protocols should incorporate plans for early monitoring of trial participants to facilitate timely evaluation and refinement of the QSP model. For instance, pharmacokinetic data and pharmacodynamic biomarker data from the initial participant(s) can be collected and analyzed promptly as they become available. Comparing these early clinical measurements against the model's predictions can confirm whether the human biological response aligns with the QSP model prediction.

- Early evaluation can enable timely model refinement and inform subsequent dose-escalation decisions within the trial. It is good practice for sponsors to include in the protocol the intention to use emerging human data to refine the model before proceeding to higher dose levels.

V. REGULATORY INTERACTIONS

When applying a QSP approach for dose selection in a FIH trial, sponsors should submit a QSP Study Report and provide documentation of methods, assumptions or uncertainties, and other information recommended in this guidance. Early interaction between sponsors and the Agency can improve model development and subsequent planning of FIH trial design. Specific development-related discussions can be helpful to ensure full alignment on the risk-based assessment, technical details on QSP modeling and evaluation, and approaches for implementation in clinical trial design. The mechanisms described below can be considered for sponsor engagement with the Agency.

A. Sponsor Meetings

Sponsors planning to use a QSP approach to determine the MABEL dose in a FIH trial should engage proactively with the Agency as early in development as possible through regulatory meetings such as the pre-IND or MIDD Paired Meetings.[5] Early dialogue facilitates mutual understanding, transparency, and efficient regulatory review during the IND submission process. In the pre-IND meeting submission or the MIDD Paired Meeting submission, sponsors are encouraged to:

- Clearly outline the intended COU of the QSP model for dose selection.

- Include a model risk assessment.

- Provide model information, at a minimum, including model structure, key assumptions, critical parameters and their bases, data sources such as literature references and study reports, and intended validation strategy. Provide transparent scientific rationale demonstrating that the model's structure, parameters, and assumptions are biologically and pharmacologically credible.

[5] For more information on MIDD Paired meetings see https://www.fda.gov/drugs/development-resources/model-informed-drug-development-paired-meeting-program.

- Provide a plan for model calibration and validation.

- Provide a plan for the model application, sensitivity and uncertainty analyses, and dose selection.

- Provide a plan for the FIH clinical trial.

- Seek early feedback on the overall approach and potential information gaps.

B. IND Submission

Sponsors intending to use a QSP approach to establish MABEL for FIH dose selection should submit the following information in their IND package:

- Intended COU of the QSP model for dose selection.

- Model risk assessment.

- Comprehensive description of the QSP model, clearly specifying the overall structure (e.g., diagram), key assumptions, mathematical equations, parameters and their values (with units), and sources of those values. Detailed documentation, including comprehensive literature references, should be submitted to substantiate both the structure and selected parameters of the model. To improve transparency and minimize bias, sponsors should include a tabulated summary of all potential parameter values obtained from various data sources, accompanied by clear rationale justifying the chosen parameter values, and should include a report of the sensitivity and uncertainty analyses. Sponsors should provide information about the computational software, software version, developed code, and data used in the model.

- Documentation of model calibration and validation. Sponsors should clearly describe the calibration methods and dataset(s) used and should present parameter adjustments transparently, including the initial parameter values, final calibrated values, and justification for any modifications made during calibration. Sponsors should summarize how calibration impacted the model's predictive capability and should provide scientific justification (e.g., biological plausibility) to support the calibration. For model validation, sponsors should include comparisons of model predictions with independent datasets not previously used in model development and calibration. Sponsors should include graphical and statistical summaries illustrating the agreement between observed and predicted data.

- Results from model application for dose selection, and sensitivity and uncertainty analyses.

- Key simulation results that clearly support the proposed dosing decisions. Typical results include, but are not limited to the following:

  - Predicted pharmacokinetic and pharmacodynamic profiles for clinical trial participants at the recommended starting dose, along with selected lower and higher doses.

  - Dose-response relationships (including uncertainty intervals) for the primary pharmacological effect or safety concern, that explicitly mark the position of the chosen starting dose within this relationship.

  - Results of sensitivity and uncertainty analyses, including a tabulated summary of parameters identified as most influential on the model predictions, accompanied by graphical representations illustrating the potential variation in predicted outcomes at the proposed dose due to uncertainty across the parameters.

- Documentation of a clear rationale for dose selection. Sponsors should clearly state the limitations of the QSP model (e.g., information gaps), along with proposed mitigation strategies or plans for additional data collection during early clinical studies. Sponsors should provide a comprehensive summary of all the considerations related to the dose selection (e.g., additional safety margins based on anticipated severity, reversibility, and clinical manageability of potential adverse effects suggested by the drug's mechanism of action; historical data from similar drugs; dose estimation based on other methods).

- A plan in the clinical trial protocol on how the QSP model will be updated based on emerging data and a plan to notify the Agency if the model updates will impact clinical decisions.