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July 24th, 2026

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Docket No. FDA-2026-D-6539; Quantitative Systems Pharmacology (QSP)-Based Dose Selection for Minimum Anticipated Biological Effect Level (MABEL) in First-in-Human (FIH) Trials

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the request for information and comments on the Agency's Draft Guidance, *Quantitative Systems Pharmacology (QSP)-Based Dose Selection for Minimum Anticipated Biological Effect Level (MABEL) in First-in-Human (FIH) Trials.*

BIO is the premier biotechnology advocacy organization representing biotech companies, industry leaders, and state biotech associations in the United States and more than 35 countries around the globe. BIO members range from biotech start-ups to some of the world's largest biopharmaceutical companies – all united by the same goal: to develop medical and scientific breakthroughs that prevent and fight disease, restore health, and improve patients' lives. BIO also organizes the BIO International Convention and a series of annual conferences that drive partnerships, investment, and progress within the sector. Learn more at bio.org.

Sincerely,

/s/
Neil Ichiro Laruan
Director, Science & Regulatory
Biotechnology Innovation Organization

General Comment(s):

BIO commends FDA for issuing this timely draft guidance and supports the Agency's continued efforts to advance the use of quantitative systems pharmacology (QSP) to inform minimum anticipated biological effect level (MABEL)-based dose selection in first-in-human (FIH) clinical trials. The draft guidance represents an important step toward incorporating mechanistic, model-informed approaches into early drug development. BIO also appreciates FDA's recognition that QSP, as a type of new approach methodology (NAM), has the potential to improve dose selection while reducing reliance on unnecessary animal testing. QSP-based MABEL represents a meaningful advancement over traditional empirical approaches, and BIO agrees that this approach should enhance, rather than replace, traditional MABEL methodologies.

Overall, BIO supports FDA's objective of providing greater regulatory clarity for the development and application of QSP-based MABEL approaches, and suggests a fit-for-purpose, risk-based validation framework as the foundation for that clarity. QSP models vary widely in their intended context of use, biological complexity, available supporting data, and regulatory impact, and the guidance would benefit from reflecting this diversity rather than expecting every model to represent the complete, relevant sequence of biological events. For example, a minimal physiologically based model developed to support an initial FIH starting dose warrants different validation and reporting expectations than a fully mechanistic model intended to justify a novel dosing regimen. A defined risk-tier framework aligned with the low/medium/high rating system in ICH M15, along with illustrative examples mapping each tier to its corresponding validation expectations, would give sponsors a more consistent basis for scoping their submissions. Additional clarity on validation expectations for QSP models built on fully human-derived or in vitro data would also be helpful, including whether and how establishing an in vitro-in vivo correlation or otherwise demonstrating predictive performance would be expected to support such models, since these approaches may not rely on translation from animal data at all. Where animal-to-human translation is used, FDA should revisit provisions that call for a uniform degree of species-specific parameterization, given the translational uncertainty involved; a qualitative discussion of species differences may be sufficient in many cases.

BIO further encourages FDA to ensure that the guidance clearly defines the intended scope of QSP-based MABEL and distinguishes recommendations related to establishing an initial FIH starting dose from broader applications of QSP throughout clinical development. Several recommendations, including elements of the Question of Interest, Model Application, and Early Monitoring and Model Refinement sections, as well as certain IND submission expectations, appear to extend into dose-escalation, regimen-optimization, and other later-stage decisions that may warrant different evidentiary standards. Greater clarity regarding terminology, context of use, and the relationship between QSP-based and traditional MABEL approaches would promote more consistent implementation, facilitate more productive sponsor-Agency interactions, and help reduce overlap with the general model-informed drug development principles already described in ICH M15. BIO recommends FDA confirm that QSP is not limited to the MABEL context when otherwise

justified and ensures that the definition of MABEL is used consistently throughout the guidance. In addition, clarification on whether the guidance is intended to apply solely to products conventionally following a MABEL-based starting dose, or whether FDA also supports integrating QSP into other starting-dose paradigms, such as the anticipated pharmacologically active dose (PAD), would be helpful where applicable.

Additional discussion of the modalities and mechanisms through which QSP-derived MABEL is likely to be most valuable, such as multispecific antibodies, immune agonists, cytokine modulators, gene therapies, and other products with complex pharmacology, would also be welcome. To support consistency across submissions, BIO recommends standard terminology, such as "QSP-enhanced MABEL" or "QSP-based MABEL," to distinguish mechanistic submissions from those relying on a traditional empirical MABEL estimate. The guidance would also benefit from consistent definitions for key terms used throughout (e.g., "estimate" versus "predict," "subtherapeutic") to avoid differing interpretations across sponsors and review divisions.

BIO also believes sponsors should retain the ability to integrate QSP-derived evidence with traditional MABEL methodologies, justifying a proposed starting dose on the totality of available evidence rather than a single prescribed approach. A sponsor with a well-characterized target and strong in vitro potency data, for example, should not need to build out a full mechanistic model if a simpler analysis already supports an adequately conservative starting dose. This same flexibility should extend to situations where QSP-derived and traditional MABEL estimates diverge; rather than defaulting automatically to the most conservative estimate, sponsors would benefit from the ability to justify a less conservative, QSP-informed dose when the strength and quality of the underlying model data support it. This flexibility matters most for programs involving novel modalities or mechanisms where the available data are inherently limited.

Regarding model updating and dose escalation, BIO recommends FDA clarify that notification to the Agency should be limited to material updates, meaning those that change, or are expected to change, dose selection, dose escalation or optimization, safety monitoring, protocol-defined decision criteria, or another clinical decision. Exploratory, confirmatory, recalibration, or other routine model updates that do not materially affect clinical decision-making should be appropriately documented but would not necessitate notification to the Agency. Sponsors would also benefit from being able to describe pre-specified model refinement plans within their IND submissions to support this streamlined approach, with confirmation that they may choose whether to continue leveraging the QSP model beyond the initial FIH starting dose, since a model developed to support that dose may not necessarily be suited, or needed, to support later-stage decisions where more empirical approaches may be sufficient.

Finally, BIO encourages FDA to keep implementation practical and sustainable for both sponsors and reviewers. Clarification and illustrative examples of what FDA expects to see for documentation, proprietary information, and software, including whether native project files from proprietary or graphical modeling platforms would be acceptable and what

confidentiality protections would apply, would be beneficial for sponsors and help streamline relevant information for reviewers. BIO also recommends that FDA accept review-sufficient documentation (i.e., documentation commensurate with the model's context of use, influence, and risk) rather than full source code, limit the "all potential parameter values" table to information relevant to the regulatory decision, and confirm that a full QSP study report is not recommended, provided that key outputs are documented in the briefing book. Internal comparator data can also raise legal and IP considerations; FDA should give sponsors flexibility, at their discretion, regarding whether such data used to justify a model parameter needs to be included in the submission.

BIO appreciates FDA's continued engagement with stakeholders as model-informed drug development evolves and offers the following recommendations to strengthen the final guidance. The comments below include both overarching recommendations and specific proposed edits to the draft guidance, intended to improve clarity, ensure regulatory expectations remain fit for purpose, and facilitate consistent implementation across sponsors.

Section	Lines	Comment and rationale	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)
General	General	Suggesting that regulators reference QSP as a type of NAM that can enable reduced reliance on animal-based models for drug development to reinforce this concept/classification.	
I	Footnote 3	Footnote 3 seems to imply that “drugs” refer to approved drugs or biologics whereas the uses of the term in the document refer to investigational drugs/biologics.	
I	25	Explicit acknowledgment that QSP approaches may support avoidance of overly conservative starting doses would be helpful. Clarifying this context could improve alignment between regulatory expectations and sponsor implementation.	"This approach has the potential to reduce reliance on animal toxicity studies and to reduce the number of patients receiving sub efficacious doses."
I	25; 185-197	The guidance promotes reducing reliance on animal studies while simultaneously emphasizing use of animal-derived PK/PD data for parameter estimation, creating uncertainty regarding expectations for human-specific targets where animal data are not informative. Language that explicitly calls out when animal data are considered insufficient would justify the use of QSP; however, this justification is undercut by language elsewhere in the guidance around defaulting to the most conservative method when approaches diverge.	Suggests FDA should clarify whether fully human-derived or in-vitro-based QSP approaches can adequately support an IND submission without reliance on animal PK/PD data, describe acceptable alternative parameterization strategies when animal data lack translational relevance, and clarify what documentation would be expected, so the animal-reduction message is operationally real. Consider also allowing sponsors to choose a less conservative QSP estimate where justified by the strength of the data used to construct the model.
I	30-32	The trigger for a QSP-based MABEL is permissive ("can, but does not necessarily") with no clear basis for when it is expected vs. optional, creating uncertainty in pre-IND interactions. The MABEL-centric title/framing risks sponsors or reviewers wrongly inferring QSP is not appropriate outside the MABEL context.	Propose to add language identifying the triggers (product class, MOA, target biology) for when a QSP-based MABEL is recommended vs. optional, and state expressly that QSP is not limited to the MABEL context when otherwise justified.
I	30-32	The scope for use of MABEL in combination with QSP	Propose to elobarate that a MABEL-based approach can be used whenever there is a risk of exaggerated pharmacology in the First in human trial due to uncertainties in biology, modality or human translatability of PKPD, and that this technology advancement is not only relevant for highly novel and high-risk concepts
II	48	MABEL definition is not consistent throughout the document. See line 53-54 versus line 82-83. Only 82-83 if needs to be measurable then also need to be able to distinguish signal from noise of assay.	Define "MABEL" and use standardized definition throughout.

II	70-71	The recommendation to consider all available data does not address differences in the relevance, quality, and uncertainty of individual data sources. Not all available data contribute equally to model credibility or confidence in the proposed FIH dose.	FDA should clarify that data integration should include an assessment of the scientific relevance, quality, and uncertainty of each data source. Suggested revision: “Therefore, a model-informed approach that considers all available and scientifically relevant data (e.g., in vitro, in vivo, and in silico), with consideration of the quality, relevance, and uncertainty of each data source, could be more appropriate to estimate a starting dose in the FIH trial.”
II/III	70-83	Although the guidance emphasizes integration of multiple data sources ("a model-informed approach that considers all available data..."), it is not explicit that QSP should complement rather than replace established MABEL approaches. Relatedly, the distinction between the QSP model's stated goal of estimating a dose expected to produce a minimal biological effect (lines 80-83) and the broader task of recommending the clinical starting dose could be further clarified.	Ask to clarify that QSP should be considered one component of an integrated MABEL assessment together with in vitro pharmacology, receptor occupancy, PK/PD, translational biomarkers, and other relevant quantitative approaches, and that the QSP-derived MABEL represents one line of quantitative evidence supporting selection of the FIH starting dose, which should ultimately consider the totality of available evidence and associated uncertainties.
II//III/IV	70-83, 267-275	In the Introduction and Background it seems to be asumed that the starting dose should always be equivalent to the MABEL. The MABEL is a benchmark on the dose-response curve so the scope of the QSP (and any other) model for FIH dose setting is to predict the full human dose-response curve including MABEL and ATD, and then argue for an acceptable PD response at the starting dose based on a risk evaluation of the totality of data.	This is discussed in line 267-275 but it would be beneficial to describe the broader scope and argumentation for a starting dose different from the MABEL earlier in the document.
III	78-120	It will be helpful to provide guidance on when QSP modeling approach is recommended over a traditional MABEL approach, and scenarios where it is optional.	Consider adding: Examples where QSP models can add value for FIH prediction include: - integrating prior preclinical and clinical data on related biology/treatments to predict biological activity of a new molecule - incorporating data from preclinical assays/models with limited translatability or narrow focus into predictions more relevant to clinical context (eg accounting for differential PK and/or in vivo target characteristics in relevant tissues)
III	81	Expand the discussion to acknowledge that QSP models can play roles beyond MABEL estimation in FIH studies, such as informing the highest efficacious dose,	"For a MABEL-based FIH dose, one of the primary goal of the QSP model is to….."

III	82	The guidance states, "the goal of the QSP model is to estimate a dose…" The use of "estimate" may cause confusion with the common use of "estimation" to refer to fitting a model to observed data, whereas "predict" may better describe the model's forward-looking function. Rather than asserting one term is correct, FDA should clarify how "estimate" and "predict" are each intended to be used and apply the chosen terminology consistently throughout the guidance.	Clarify the intended distinction between "estimate" and "predict" as used throughout the guidance (e.g., "the goal of the QSP model is to estimate/predict a dose…"), and apply the chosen terminology consistently.
III	88-89	Inclusion of all available data may not improve model performance and may increase complexity and computational burden. Additional biological detail not directly relevant to the key question may not improve predictive accuracy. Emphasizing “critical” data supports a fit-for-purpose approach aligned with current QSP practices.	"Integration of All ~~Available~~ Critical Data: A foundational principle for QSP modeling is to consider all relevant data for dose prediction. This can includes in vitro studies….."
III	88-95	The draft guidance refers to in vitro studies, including target binding affinity, receptor occupancy and activation, and cytokine release assays. While these are important examples, they may not capture the full range of functional assays relevant to complex therapeutic modalities or mechanisms of action. For some products, functional assays that characterize secondary mechanisms of action, indirect pathway effects, immune-cell engagement, cytotoxicity, cell-state changes, downstream signaling, biomarker modulation, or tissue-specific responses may be important for QSP model development and MABEL dose selection.	Propose the Agency broaden the text to read: “...in vitro studies, including, but not limited to, assays in human cells or tissues characterizing target binding affinity, receptor occupancy, receptor or pathway activation, cytokine release, downstream signaling, functional pharmacology, secondary mechanisms of action, and other relevant direct or indirect biological effects...”
III	97-100	Accounting for species-specific parameters in a QSP model, which is typically developed to predict human physiology, is not trivial and carries a high degree of translational uncertainty. While the draft guidance appropriately emphasizes accounting for species differences and scaling to humans, it would benefit from further clarifying that sponsors should describe the assumptions, rationale, and limitations underlying the selected inter-species translation or scaling approach, particularly where species differ in target expression, binding affinity, cellular context, immune-system biology, pharmacodynamic response, or downstream pathway activity.	Propose the Agency revise the text to read: “When translating nonclinical data to humans, sponsors should describe the rationale for the selected inter-species scaling approach, key assumptions supporting the translation, species-specific parameters used in the model, and the potential impact of uncertainty in these assumptions on predicted human dose-response relationships.” If this level of detail is not feasible for a given CoU, FDA should clarify that a qualitative discussion of species differences is acceptable.

III	100	Clarify whether “scaling” is intended to be addressed in this section and, if so, consider expanding the discussion to reflect this topic. Rationale: The section references scaling in the heading but does not clearly address scaling considerations within the text. Clarifying the intended scope or aligning the content with the heading would improve clarity.	
III	102 - 108	The expectation that QSP models represent the "complete, relevant sequence of events" (lines 102-108) may be interpreted as requiring excessive model complexity. Representing the complete sequence of biological events may not be feasible or practical, and real-world QSP models are typically fit-for-purpose, not exhaustive. Excessively complex models may also reduce interpretability and practical identifiability.	Suggest to revise the text to state that QSP models should adequately represent the relevant biological processes necessary for the intended context of use, using a parsimonious, fit-for-purpose approach, rather than the complete biological system, and clarify that model complexity should be proportional to the Context of Use (CoU), model risk, and available biological knowledge. Separately, clarify that reporting requirements (distinct from model complexity) should also be proportional to model risk: lower influence/consequence applications should not require the same rigorous reporting as higher influence/consequence applications.
III	102-108	FDA should refine this section to clarify, that when feasible, the biological response modeled should be one relevant to known/hypothesized safety risks, especially if safety and efficacy are associated with different cell types, tissues, or drug pathways. Rationale: For example, for a T cell engager safety considerations may be more associated with cell killing in normal cells/tissues or cytokine release, while efficacy may reflect cancer cell elimination in tumor tissue. The difference between biological responses associated with safety vs. efficacy can also be considered when addressing under-dosing/dose escalation needs in lines 267-75.	
III	103	Remove “complete” to avoid implying full mechanistic representation. Rationale: The expectation of complete mechanistic representation may not be necessary or feasible in all cases. Removing this term supports a fit-for-purpose approach while maintaining flexibility in model development	"In general, QSP models should represent the ~~complete,~~ relevant sequence of events from……"
III	104-105	"and distribution to molecular target engagement, activation of signaling pathways, and subsequent biological responses."	Suggest to change: "distribution to site of action, target engagement, and subsequent biological response." The signaling pathway could be considered part of the biological response, and the QSP model should include granularity based on how much is known about the MoA and the data available for model development.

III	106	“Expression level of the molecular target and its turnover”	Suggested change to “expression level of molecular target and its dynamics (such as turnover)”. This makes the language more general and includes mechanisms like shedding under the broader description of “dynamics.”
III	110-115	Clarify that expectations for iterative refinement apply in cases where the QSP model is intended to be used beyond initial FIH dose selection. Rationale: The discussion of iterative refinement appears in the context of FIH dose selection, where clinical data are not yet available. In practice, QSP models developed to support initial dose selection may not be used beyond this decision point. Clarifying the intended scope of iterative refinement would improve alignment with typical use of QSP in early development.	
III	114-115	Clarify that differences between model predictions and clinical data may be addressed through explanation and contextualization, in addition to model refinement. Rationale: The current discussion appears to emphasize model refinement when differences between predictions and clinical observations arise. In practice, such differences may also be explained by underlying assumptions, population differences, study design, or limitations in available data, without necessitating further model refinement. Clarifying that explanation and contextualization represent acceptable approaches, where appropriate, would better align with typical application of QSP in early development.	
III	114-117	The guidance encourages incorporation of emerging clinical data into model refinement, stating that “refining the model is especially crucial when early clinical data contradict model predictions” and that this allows for “real-time updating of model assumptions... and adaptive decision-making.” However, the QSP model is primarily useful for setting the first dose; it is less useful for subsequent doses, where dose escalation is typically driven by clinical judgment. Use of immature early clinical datasets to trigger model refinement may introduce bias and lead to premature model updatess. Early discrepancies between observed data and predictions may simply reflect limited sample size or population heterogeneity rather than a flawed model.	Recommend deleting the referenced text on real-time updating and instead clarifying that model refinement should be considered when new mechanistic insights or sufficiently mature, meaningful clinical data are available (not with each dose level), unless emerging data may meaningfully change model recommendations. FDA should not force sponsors to submit model updates at every dose level where the model's stated purpose is limited to setting the first dose.
IV	128	Consider revising the phrase “doses for FIH trials that are safe but not subtherapeutic” may benefit from revision as QSP-predicted doses may be lower than the eventual Recommended Phase 2	"…doses for FIH trials that are safe but not subtherapeutic and expected to deliver minimal biological activity."

		Dose (RP2D) and could be perceived as subtherapeutic depending on the definition applied.	
IV	128-129	"Sponsors should provide the following information in their submission when using QSP for dose selection in FIH trials:"	The requirements for interactions and submissions are addressed in Section V. Suggest modifying the sentence to "Sponsors should consider the following information when using QSP for dose selection in FIH trials."
IV	135-138	Given that QSP can be considered a type of novel approach method, it would be good to cross-reference the "General Considerations for the Use of New Approach Methodologies in Drug Development" draft guidance previously issued to ensure consistency across general tone, language, and definition of terms (i.e., CoU) etc.	
IV	137	(...and clarify what other information will be used in the model.) This does not seem to align with the ICH M15 wording, which mentions "...and any additional data or evidence that will inform the answer to the question of interest."	Suggest using the following ICH wording verbatim: "...and any additional data or evidence that will inform the answer to the question of interest."
IV	140-151	Clarify how model influence and consequence of decision are intended to inform expectations for model validation and documentation. Rationale: While the guidance introduces concepts such as model influence and consequence of decision, it does not clearly describe how these concepts translate into practical expectations for model validation and documentation. Clarification would support consistent application and align with the decision-focused framework described in ICH M15.	
IV / V	140-151; 323	The draft guidance adopts the ICH M15 concept of model risk assessment (the two-factor influence × consequence concept) but does not provide a standardized risk-tier framework or evaluation matrix (e.g., low/medium/high). Without clear categorization of model influence and decision consequence, sponsors and review divisions may apply inconsistent validation expectations.	FDA should establish explicit model risk tiers (e.g., low, medium, high) aligned with ICH M15 grading, describe corresponding validation expectations for each tier, and provide one or two practical examples illustrating low-, medium-, and high-risk contexts of use for QSP-supported MABEL determination, mapping risk tier to validation expectations to ensure more rigorous requirements for higher risk/consequence applications and better consistency across sponsor submissions. Where the guidance separately instructs sponsors to "include a model risk assessment" (line 323), FDA should make explicit that this means an assessment conducted in accordance with ICH M15.

IV	148	(Consequence of making a wrong decision...) Seems incomplete.	Suggest using full ICH M15 wording: “The consequence of wrong decision refers to the potential negative effect (e.g., on patient safety and/or lack of efficacy) resulting from an incorrect decision based on all available information.”
IV	149-151	"The mechanism of action and anticipated safety profile of a drug can impact the consequence of making a wrong decision."	Suggested Change: "The drug's mechanism of action and the desired safety profile can influence the consequence of making a wrong decision."
IV	150-151	Lines 150-151 state that the mechanism of action and anticipated safety profile of a drug can impact the consequence of making a wrong decision. They may be more likely to impact the risk of making a wrong decision than to impact the consequence of the wrong decision	"anticipated safety profile of a drug can impact the ~~consequence~~ risk of making a wrong decision."
IV	153-163	Largely repeats what was already said in lines 88-95 and 102-108	
IV	159-163		Suggest to shift the expectation from an attempt to include everything in the model to a focus on those processes that are relevant to the question of interest.
IV	160	For biologics and cell-engaging therapies, consider adding target-cell abundance, receptor turnover, effector-cell abundance and target mediated drug disposition in the critical components to be identified.	".. cells, biomarker turnover dynamics, target-cell abundance, receptor turnover, effector-cell abundance, target-mediated drug disposition, downstream pathways, protein binding,.."
IV	162-163	“The model should incorporate multiple biological subsystems to reflect potential pharmacological effects and safety concerns.”	Clarify that including multiple biological subsystems is only appropriate when there is sufficient mechanistic understanding of the underlying pharmacology or safety concerns. In cases where the mechanism driving a safety signal is not well understood, incorporation into a QSP model may not be feasible or scientifically justified.
IV	172	Evaluation of alternative hypotheses and model structures may not always be feasible or scientifically justified, particularly in early development where mechanistic understanding is limited. Exploration of multiple alternative models can also introduce significant resource burden without clear benefit. Sponsors may instead justify the selected model structure, document assumptions and limitations, and validate predictions against available data.	"Evaluations should be conducted, if ~~possible~~ feasible and scientifically justified,… "
IV	172-174	The draft recommends evaluating alternative model structures “if possible.” Sponsors should not be expected to evaluate speculative structures that are not biologically plausible, supported by available evidence, or reasonably expected to affect dose selection or safety conclusions.	FDA should clarify that alternative model structures should be evaluated when they are biologically plausible, supported by available evidence, and reasonably expected to materially affect dose selection, safety conclusions, or another decision within the model's context of use.

IV	179	Consider adding immune environment differences between in vitro and in vivo systems, and among different species, to this bullet point.	"For biological products, it is especially critical to recognize that target interactions and immune responses can differ significantly between species and, immune environment can differ between in vitro and in vivo systems, and among different species."
IV	179-183	The potential species differences in immune responses and target interactions should be relevant for biological products, as well as synthetic drugs.	
IV	182	Recommend deleting the phrase 'monoclonal antibodies'. Not necessarily "monoclonal antibodies" only, bi-specific and tri-specific etc. can have human-specific targets as well.	
IV	185-197	Novel approach methods may exist that can be included to offer human-relevant data, especially for pharmacodynamic parameter estimation. Calling these out explicitly can ensure it's understood that NAMs (beyond humanized in vivo preclinical species models – i.e., in vitro, ex vivo) should be considered, as appropriate.	"Animal-based studies or other nonclinical studies, including novel approach methods, can be used to estimate parameters for..."
IV	197	The recommended addition to the text allows flexibility where parameter distributions are uncertain but transparently documented.	"be accounted for in the models if known, or clearly described within model assumptions and considered within the risk assessment framework."
IV	210-218	Given that QSP can be considered a type of novel approach method, it would be good to cross-reference the "General Considerations for the Use of New Approach Methodologies in Drug Development" draft guidance previously issued to ensure consistency across general tone, language, and definition of terms (i.e., model validation) etc. Additionally, given the desire to enable human-relevant predictions, suggesting that, when feasible, sponsors should evaluate the model prediction against data collected in clinical and nonclinical studies can be limiting. Clinical data may be very limited, if available at all, and nonclinical study data (i.e., in vivo studies in preclinical species) may be lacking in human-relevant predictivity/translatability, even if pharmacologically relevant preclinical species exist, due to other inter-species variables beyond our current understanding. Suggesting to better clarify when such model predictivity evaluations "should" be done to account for such instances.	

IV / V.B	212-214; 360-368	The draft guidance does not adequately explain what may substitute for independent/analog validation when none exists — for example, whether a model built on "gold standard" data that has been successfully used for translation in other systems would be sufficient, and whether such evidence could justify a dose less conservative than suggested by MABEL. This is particularly relevant for compounds with no clinical precedent, where it will not be possible to create datasets to validate model predictions; calibration datasets may be available, but validation in these cases will be more related to verifying mechanistic plausibility.	FDA should articulate an explicit fit-for-purpose validation framework so that mechanistic plausibility and other scientifically appropriate evidence can substitute where external/analog validation is not possible, with FDA providing flexibility for compounds lacking clinical precedent to support the broader applicability of the guidance. When independent validation data are unavailable, model verification, calibration, mechanistic plausibility, and appropriately mature emerging clinical evidence may contribute to establishing credibility for the defined context of use. FDA should also revise line 220 from "After successful validation" to "After model credibility has been established for the defined context of use."
IV	216-218	The draft relies on data from similar molecules and other datasets (for integration and validation) but says little about the legal boundaries or data-use implications of doing so.	Ask FDA to clarify language around what kind of comparator data is allowable. Any datasets that are in the public domain for comparators should be allowable, but internal data generated with a comparator compound may pose legal risk, especially if the data contradict what is in the public domain.
IV	220-227	Suggesting to clarify definition of "successful validation" since prior draft guidance ("General Considerations for the Use of New Approach Methodologies in Drug Development") notably stated that validation wasn't required for NAMs (such as QSP) to be leveraged.	Suggesting to align guidance provided in "general considerations for the use of NAMs…" draft guidance regarding validation requirements to leverage QSP as a NAM. Suggested specific edit: "Model Application: ~~After successful validation,~~ Assuming consideration and demonstration of validation principles outlined in "General Considerations for the Use of New Approach Methodologies in Drug Development" intended to enhance the interpretability and reliability of QSP as a NAM, the model can be applied to predict the drug respones under different dosing regimens."
IV	225	Clarify how qualitative descriptors such as "steep" and "shallow" should be interpreted in this context. Rationale: The use of qualitative descriptors such as "steep" and "shallow" may be subject to varying interpretation. Clarification on how these terms should be interpreted, or the factors that define them in this context, would support consistency in evaluation.	"A gradual ~~(shallow)~~ response at low doses can support selection of a slightly higher initial dose, whereas a pronounced ~~(steep)~~ increase in response..."

IV	229-239	Consider reinforcing in this section that sensitivity and uncertainty analyses should be interpreted in terms of their impact on decision-making for the proposed FIH starting dose. While later sections link model outputs to decision-making, the discussion of sensitivity and uncertainty analyses in this section focuses primarily on identification of influential parameters and sources of uncertainty. Reinforcing their role in informing decision consequences for the proposed FIH starting dose would improve clarity and consistency across the guidance.	
IV	231-232	Evaluation of alternative hypotheses and model structures may not always be feasible or scientifically justified, particularly in early development where mechanistic understanding is limited. Exploration of multiple alternative models can also introduce significant resource burden without clear benefit to the decision being supported. Sponsors may instead justify the selected model, document assumptions, and validate predictions against available data. Clarifying that such evaluations should be applied where feasible and relevant would improve alignment with practical QSP application.	"Sponsors ~~should address model structural uncertainty by~~ may consider evaluating alternative biological hypotheses and model architectures~~.~~, where feasible, scientifically justified, and relevant to the decision being supported."
IV	239	Sensitivity and uncertainty analyses are important components of model-informed drug development and should be conducted and communicated transparently to the Agency. However, these analyses should not lead to a default selection of the most conservative or lowest possible dose solely based on modeled scenarios. Rather, their role is to contextualize model robustness, identify key drivers of variability, and support an informed, balanced interpretation of the data.	Add the following statement at the end of the paragraph: "Testing for sensitivity and uncertainty does not necessarily imply that the most conservative or lowest plausible scenario should determine the proposed starting dose; rather, dose selection should be guided by physiological relevance, the totality of available data, and appropriate scientific justification, with the impact of uncertainty addressed within the model risk assessment framework."
IV	241-275		"- recommend to clarify the methodologies used should be relevant to the clinical or disease setting; - suggestion on writing: the concerns are mixed in different paragraphs, suggest to remove the first sentence in line 258 '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."

IV	245-275	The draft guidance directs sponsors to default to the lowest (most conservative) dose estimate when QSP and traditional MABEL approaches produce discordant results, particularly for novel targets lacking clinical precedent. While a conservative approach to FIH dose selection is appropriate to protect trial participants, this establishes a methodological hierarchy in which conventional MABEL approaches are implicitly prioritized over QSP predictions, irrespective of the assessed model risk. It is difficult to reconcile with the risk-based principles of ICH M15, under which the required level of confidence in a model should be commensurate with its context of use, model influence, and the consequences of an incorrect decision, rather than a default preference for one methodology. Defaulting to the lowest dose also undermines a central benefit of QSP, avoiding unnecessarily prolonged escalation from doses that are too low, and is in tension with the guidance's own allowance for oncology and other life-threatening indications to start above the absolute MABEL. Additional clarity is needed on what constitutes a "substantial" difference between QSP-derived and traditional MABEL estimates, and on the definition of "novel target lacking clinical precedent" (including whether novel payloads or modalities fall within this category).	Recommend the Agency frame these recommendations around the overall model risk assessment rather than target novelty alone. When QSP and conventional MABEL approaches yield discordant dose estimates, FDA should provide a structured framework allowing sponsors to investigate and justify the biological and mechanistic basis for the discrepancy, including justification of a QSP-derived starting dose higher than suggested by traditional MABEL, particularly for lower risk/consequence applications, with the level of additional evidence and conservatism commensurate with the assessed model risk and potential consequences of an incorrect decision, rather than automatically defaulting to the lowest estimate. FDA should also clarify the definition of "novel target lacking clinical precedent," clarify what constitutes a "substantial" difference between QSP-derived and traditional MABEL estimates, and provide illustrative examples of circumstances where a starting dose above absolute MABEL may be justified and how benefit-risk factors should be weighted in that decision.Relevant factors could include disease severity, lack of effective alternatives, expected subtherapeutic exposure at lower doses, the predicted minimal active dose, dose-response uncertainty, safety mitigations, staggered enrollment, sentinel dosing, and real-time PK/PD monitoring.
IV	247	A traditional MABEL estimate is stated to be one based on in vitro pharmacological activity - this is not a universal approach. Any combination of in vitro and in vivo PKPD modelling may be used to predict the human dose-response incl. the MABEL.	
IV	247	The magnitude of 'substantial differences' between QSP-based and traditional MABEL estimates may influence the level of rationale expected to support the proposed dose. Clarification would support consistent application.	"Additional ~~caution is~~ justification may be warranted when a QSP-based dose differs substantially from traditional MABEL estimates. The level of justification should be commensurate with the magnitude of the difference and the potential impact on patient risk."
IV / V	262; 393	The guidance references "anticipated severity, reversibility, and clinical manageability of potential adverse effects"	Suggest adding "monitorability" to this list in both locations: "anticipated severity, reversibility, monitorability, and clinical manageability."

IV	262-265	Provide clarification on the intended application of the safety margin. For example, specify whether safety margins are to be applied to dose and/or other relevant metrics, including, but not limited to, exposure, receptor occupancy, and biomarker response.	" 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. Such margins may be applied to the dose or other model-derived metrics relevant to the identified risk and should be justified in the context of the proposed dose-selection strategy."
IV	271-275	Provide additional context or examples for scenarios where initiating above MABEL may be appropriate. This represents a high-impact decision point, and clearer criteria would support consistent interpretation and application.	"In some cases, starting at a minimal active dose that is higher than the MABEL may be justified. Factors that may support such a decision include the severity of the disease, the limitations of traditional MABEL approaches, the availability of relevant mechanistic or clinical comparator data, and the strength of evidence supporting the QSP model prediction."
IV	272	Consider revising "can help determine" to "may help determine" the minimal active dose. The current wording may overstate the certainty of QSP model predictions, whereas the impact of QSP on dose selection can vary depending on the context and may not always result in a higher predicted dose than traditional approaches.	Change to "QSP models may help determine that minimal active dose".
IV / V	287-399 (incl. 296, 331)	The draft guidance encourages iterative model refinement but does not clearly differentiate updates requiring FDA notification from updates that can be managed within existing IND processes, and appears to assume the model will be used in an adaptive manner, which may not always be the case. The guidance further recommends that sponsors include in the protocol the intention to use emerging human data to refine the model before proceeding to higher dose levels (line 296), and separately recommends a plan in the clinical trial protocol for how the QSP model will be updated and a plan to notify FDA if updates impact clinical decisions (lines 397-399). These protocol-level requirements may often be impracticable, once clinical data are available, clinical results (and the existing flexibility of dose-escalation rules in the study protocol) should drive dose-escalation decisions, and the required model revalidation could become an unworkable limitation. Relatedly, the guidance does not clarify the expected level of detail for modeling plans (lines 331 and 397-399) at the pre-IND, MIDD Paired Meeting, and IND stages, or whether such plans are intended to be binding versus a prospective framework that may evolve as new data become available.	FDA should clarify which QSP model updates warrant FDA notification, which can proceed under existing IND provisions, and whether pre-specified model refinement plans submitted with initial IND application may serve as advance authorization for defined categories of updates, adjusting the adaptive-trial framing to accommodate other circumstances. We recommend striking lines 296 and 397-399, which would require the protocol itself to describe model-update and FDA-notification plans; this content, if needed, is more appropriate for a QSP analysis strategy document than the clinical protocol. For the modeling plans referenced at lines 331 and 397-399, we propose the following clarifying language: "Modeling plans should describe the intended analyses, key data sources, model-development and validation strategy, planned sensitivity and uncertainty analyses, and how emerging data may be incorporated. These plans are expected to provide a prospective framework for regulatory discussion and review, but may be refined as additional data become available, provided that changes are scientifically justified and appropriately documented."

IV	297	Line 297: change "before proceeding to higher dose levels" to "as higher dose levels are explored". Model refinement should not be required prior to dose escalation.	Change "before proceeding to higher dose levels" to "as higher dose levels are explored".
V	301-390	The guidance is inconsistent regarding whether a QSP study report is expected: it references a QSP study report in the “Regulatory Interactions” section (line 304), but then lists all IND-package expectations for QSP modeling (line 340, Section V.B) without requesting a study report. It would help sponsors to clearly state if/when such a report is actually required. Separately, the guidance provides detailed recommendations on model documentation content but does not recommend a standardized report structure.	FDA should clarify whether and under what circumstances a QSP study report is expected. A formal report should not routinely be warranted when the key methods, assumptions, uncertainties, outputs, and dose-selection rationale are adequately documented in the briefing book or IND submission. When FDA determines that a report is warranted, its content and level of detail should be commensurate with the model's context of use, influence, and risk. FDA should consider providing an example report template to promote consistency across submissions.
V	314-319	Suggesting to further clarify earliest opportunity/mechanism and required plan/data for early engagement of sponsor with regulators on QSP-enabled approach to determine MABEL dose in a FIH trial to ensure alignment with prior issued draft guidance (“General Considerations for the use of New Approach Methodologies in Drug Development”) and other guidance informed on by the FDA (ICCVAM Validation Workgroup’s “Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies”).	This guidance notes leveraging pre-IND and MIDD meetings for early regulatory engagement. Prior draft guidance ("General considerations for the use of NAMs…") noted engagement with the applicable review division is encouraged when there is uncertainty about the suitability of a method for regulatory use when considering use of a NAM believed to be suitable, adequate and feasible for a proposed regulatory use. Additionally, FDA/CDER have instructed that INTERACT and CIPM meetings can be leveraged as mechanisms to gain insight into suitability of NAMs use for regulatory use. Suggesting that the agency clearly articulate which is the earliest feasible mechanism and maintain that for NAMs discussions, which would most likely be INTERACT, not pre-IND or MIDD. Suggested specific edit: "Sponsors planning to use a QSP approach to determine the MABEL dose in a FIH trial should engage proatively with the Agency as early in development as possible through regulatory meetings such as the INTERACT, pre-IND or MIDD Paired Meetings."
	314-319	The guidance encourages early engagement but focuses primarily on Pre-IND and MIDD meetings.	FDA should explicitly identify INTERACT meetings and other informal engagement mechanisms as acceptable avenues for early discussion of QSP approaches.
V	327-328	Consider providing additional detail on criteria for model credibility, aligned with ICH M15 principles. Rationale: The ICH M15 guideline provides a general framework for assessing model credibility, but more specific clarification on how these principles	

		are applied in practice would support consistent evaluation across submissions.	
V	331-334	"Provide a plan for model calibration and validation… Provide a plan for the model application, sensitivity and uncertainty analyses, and dose selection."	Clarify if a formal MAP is expected for QSP analyses and suggest a template. Clarify what is expected by "plan for the model application" — is this a description of simulation scenarios to support dose selection?
V	336	"Provide a plan for the FIH clinical trial."	Need additional clarity around what is exactly recommended here; is this the FIH protocol, some kind of abbreviated protocol, or something else?
V	336	The guidance encourages model refinement using emerging clinical data. FDA should describe when a model update requires FDA notification and what changes would trigger a protocol amendment. The FDA should clarify expectations for how information related to QSP model application should be incorporated into the FIH clinical trial plan, including what aspects of model use or decision-making should be prospectively specified in the protocol. Rationale: The guidance recommends providing a plan for the FIH clinical trial but does not clearly describe whether sponsors are expected to include plans related to model refinement, use of emerging clinical data, or other QSP-informed activities. Clarification would support consistent preparation of meeting packages and regulatory submissions.	Change line 336 to "Provide a plan for the FIH clinical trial, including plans for refining the QSP model with emerging data and any potential trial modifications that will be based on the refined model."
V	357	Clarify expectations regarding the information that should be provided about developed code used to implement the QSP model. Rationale: Expectations regarding submission of model code versus summary documentation are not clearly defined. Clarification would support consistent preparation of submissions and efficient regulatory review.	"Sponsors should provide information about the computational software, software version, ~~developed code,~~ and data used in the model, along with a concise description of the model implementation and any developed code relevant to interpretation of model predictions."