



Original Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Early Clinical Development Can Be Designed Around Mechanistic Falsification Instead of Sequential Confirmation

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ABSTRACT

Early clinical development is commonly organized as an accumulation of favorable observations: adequate exposure, target engagement, pharmacodynamic activity, tolerability, and eventually evidence of clinical benefit. That sequence is operationally useful but can create an inferential problem when each positive result is treated as another layer of confirmation without specifying which mechanistic claim has actually survived a credible opportunity to fail. This Perspective proposes a different design principle. Early human development can be structured around explicit mechanistic claims that are interrogated at separable levels: whether relevant exposure is achieved; whether the intended target is engaged at the relevant site and time; whether engagement produces the predicted pharmacodynamic consequence; and whether that consequence remains meaningful in the biological and clinical context of the treated population. Under this approach, discordant evidence is used to localize uncertainty rather than being absorbed into a generally favorable narrative. Failure may implicate delivery, target engagement, pathway sufficiency, biomarker validity, disease context, dose, timing, or the therapeutic hypothesis itself. The proposed falsification-centred architecture does not constitute a prospectively validated development algorithm. Its purpose is to make early clinical programs more explicit about what individual observations can falsify, what they cannot establish, and why mechanistically positive evidence may still leave the central therapeutic hypothesis unresolved.

Keywords: Early clinical development, Mechanistic falsification, Target engagement, Pharmacodynamic biomarkers, Model-informed drug development, Dose escalation

Received: 24 August 2026; **Revised:** 04 October 2026; **Accepted:** 09 October 2026

INTRODUCTION

Drug development has increasingly emphasized disciplined questions about target biology, tissue exposure, safety, patient selection, and the relationship between pharmacology and disease. The AstraZeneca 5R experience illustrated the value of organizing programs around explicit scientific dimensions rather than assuming that advancement through development phases itself demonstrates technical validity. Model-informed drug development extends this logic by integrating pharmacokinetic, pharmacodynamic, disease, and trial information, while analyses of development-transition decisions show that progression remains a multidimensional judgment rather than the output of a single evidentiary rule [1–3]. The US Food and Drug Administration's MIDD program further demonstrates that quantitative models can become formal objects of regulatory-scientific discussion, although such interaction is not equivalent to regulatory endorsement of a model-derived conclusion [4].

Early-development language nevertheless remains strongly confirmatory. Programs seek evidence that exposure is adequate, the target is engaged, a biomarker changes, and clinical outcomes move in the desired direction. Each finding may be useful, but positive observations can accumulate faster than the dependencies among them are resolved. Adequate plasma exposure does not necessarily establish exposure at the site of action. Target engagement does not establish downstream pathway sufficiency. A pharmacodynamic response does not establish clinical relevance.

This Perspective proposes that early development be reorganized around mechanistic falsification. The proposal is not that one negative result should terminate a program, nor that complex biological hypotheses can be falsified by a single experiment. Rather, a therapeutic hypothesis should be decomposed into linked claims whose failures have different meanings. Development then becomes an effort to determine which claims have survived informative tests and where uncertainty remains. Discordance is consequently treated as evidence capable of localizing failure rather than as noise that must automatically be explained away.

The confirmation-first development paradigm

Probability-of-success methods were developed partly to make development decisions more explicit and quantitatively defensible. Bayesian approaches can integrate heterogeneous evidence and expose assumptions underlying program-level estimates [5]. Yet definitions, methods, and applications of probability of success remain heterogeneous across drug development [6]. A single probability may therefore combine uncertainties that are mechanistically distinct: whether the molecule reaches the relevant compartment, whether it modulates the intended target, whether target modulation changes downstream biology, whether the biomarker is valid, and whether the treated population depends on that mechanism.

The term confirmation-first development paradigm is used here as a proposed analytical description, not as an established label for industry practice. Its defining problem is not the collection of positive evidence. It is the tendency to treat sequential positive observations as mutually reinforcing without preserving their conditional structure. A systemic concentration can be called adequate despite uncertainty about tissue penetration; an indirect biomarker can be treated as engagement; and a downstream biological change can be interpreted as validation even when parallel pathways could produce the same signal.

A falsification-centred design asks a different question: what observation, obtained under an adequately informative condition, would make the current mechanistic interpretation untenable? Probability estimates can still be used, but they become summaries of explicitly interrogated claims rather than substitutes for specifying what could fail. Evidence becomes valuable not only because it supports continuation, but because it discriminates among competing explanations.

Defining mechanistic claims

Mechanistic falsification requires a mechanistic claim precise enough to test. Pharmacological characterization cannot be reduced to the statement that a molecule “hits” a target. Drug action can depend on ligand efficacy, signaling pathway, receptor state, cellular environment, concentration, kinetics, tissue distribution, and assay system [7]. An early-development claim should therefore specify the intervention, intended target or process, direction of perturbation, relevant site, temporal condition, and expected downstream consequence.

Human genetics can strengthen the prior plausibility of a target hypothesis by linking naturally occurring perturbations to disease biology [8]. Historical analyses likewise associate genetic support with greater development success, although that relationship is probabilistic rather than deterministic [9]. Genetic evidence therefore changes prior confidence; it does not establish what a particular molecule does in a treated patient at a finite dose.

Safety claims require the same discipline. Human genetics can inform hypotheses about possible on-target consequences [10], but inherited lifelong variation is not equivalent to pharmacological modulation initiated later in life. Genetic phenotypes also cannot reproduce every consequence of drug selectivity, tissue distribution, exposure pattern, or off-target activity.

For this Perspective, a mechanistic claim is therefore proposed to contain seven linked elements: intervention, relevant exposure, target or process, site of action, temporal condition, proximal biological consequence, and clinically relevant downstream implication. Making those elements explicit creates separable failure states. A molecule may fail to reach its required site, reach that site without engaging the target, engage the target without propagating the expected signal, or produce the signal without affecting disease-relevant physiology. These failures should not be interpreted as equivalent.

Exposure as a necessary test

Exposure is the first necessary test because downstream mechanistic inference is difficult to interpret when the drug has not been delivered at an informative concentration for an informative duration. First-in-human dose selection for immunomodulators increasingly integrates pharmacology, pharmacokinetics, pharmacodynamics, toxicology, and mechanistic risk rather than relying on a single starting-dose construct such as MABEL [11]. T-cell engaging bispecific antibodies similarly require starting dose and escalation to be considered jointly with exposure, pharmacology, and safety because excessive pharmacology can itself constrain the range in which a mechanism can be tested [12].

For falsification, however, “exposure achieved” is not a context-free state. Systemic concentration may be necessary but insufficient when activity depends on penetration into a specific tissue or compartment. PBPK analysis coupled with PET-guided verification of tyrosine kinase inhibitor distribution illustrates how target-site exposure can require evaluation beyond conventional plasma pharmacokinetics [13].

This distinction changes the interpretation of failure. If target engagement is absent while relevant site exposure remains uncertain, the negative engagement result cannot cleanly falsify the biological target. It may instead challenge the delivery strategy, formulation, dose, schedule, or exposure model. Exposure therefore acts as an interpretability prerequisite for the next mechanistic gate rather than as independent confirmation that the therapeutic hypothesis is correct.

Target engagement as a falsification gate

When informative exposure has been established, target engagement can provide the first direct test of whether the molecule performs the pharmacological action on which the program depends. In the first-in-human study of the CXCR7 antagonist ACT-1004-1239, dose-dependent changes in CXCL12 were used as a target-engagement biomarker, linking human exposure to intended target biology [14]. The importance of such evidence lies in its ability to narrow plausible explanations for the drug's observed behavior.

That narrowing depends on what is actually measured. Modeling of checkpoint inhibitors has shown that dose selection based on target engagement can differ from selection based on inhibition of receptor-ligand interaction [15]. Metrics that appear to describe the same mechanism can therefore answer different questions. Indirect biomarker evidence, physical occupancy, functional inhibition, and downstream pathway suppression should not be treated as interchangeable unless their relationships are established for the relevant system.

Model transfer introduces another boundary. Anti-TIGIT dose selection has used knowledge derived from co-expressed PD-1 inhibitor target engagement to inform projections for TIGIT-directed therapy [16]. Such borrowing can be useful when direct human measurements are limited, but its inferential strength depends on assumptions about cross-target relationships and the context in which they were calibrated. Model-transferred engagement evidence should therefore remain distinguishable from direct human measurement.

Orthogonal evidence can strengthen the interpretation. A placebo-controlled phase 1 study of active immunotherapy against pathological α -synuclein demonstrated measurable immunogenicity and target-related biological responses without thereby establishing clinical disease modification [17]. In the phase 1 OMO-103 study, pharmacokinetic information and tumor transcriptomic analyses jointly supported perturbation of MYC-related biology [18]. These cases illustrate why engagement is most informative when the measurement is mechanistically proximal and, where feasible, supported by independent evidence.

The asymmetry of the gate is central to the proposed architecture. Failure to demonstrate engagement under adequate site exposure with a sufficiently informative assay can strongly challenge the molecule-target claim. Positive engagement establishes much less. It shows that one necessary link has survived testing but leaves unresolved whether the perturbation is sufficient, whether the pathway propagates the expected signal, whether compensation attenuates it, and whether the disease depends on that biology.

The evidentiary dependencies are easier to distinguish visually than in a sequential narrative; **Figure 1** therefore places target engagement between an exposure-eligibility boundary and several downstream uncertainties rather than depicting it as a milestone that automatically advances the program.

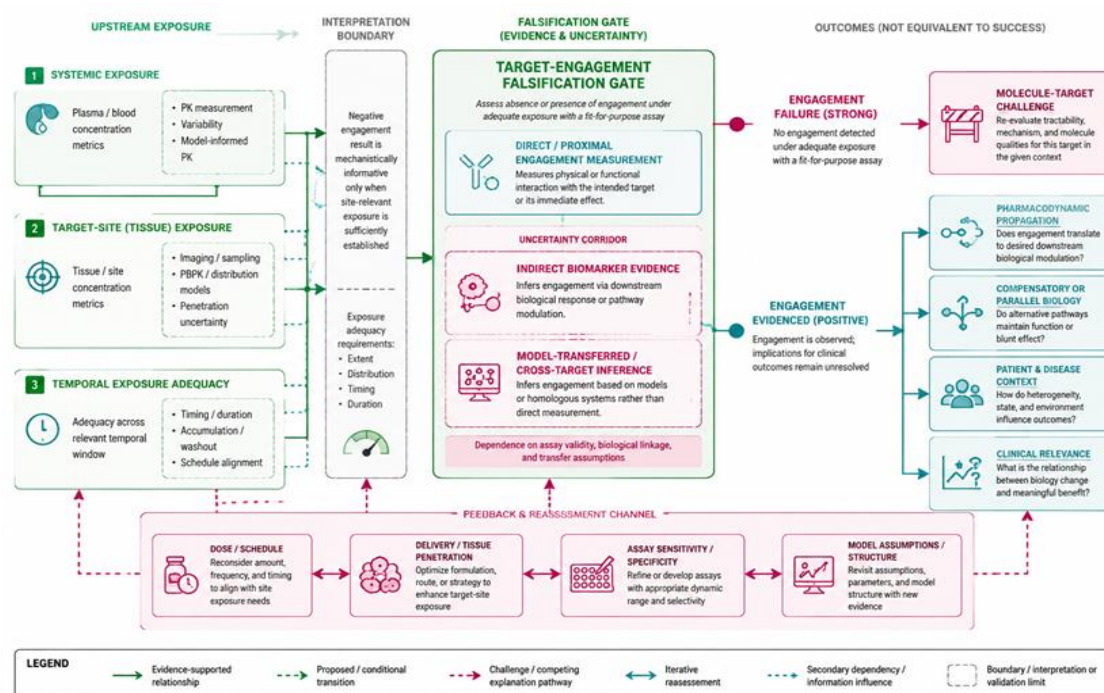


Figure 1. Target-Engagement Falsification Field Across Exposure, Biomarker Utility, and Downstream Uncertainty

Pharmacodynamic response

Target engagement establishes that the intended interaction has occurred; pharmacodynamic response asks whether that interaction propagates into the predicted biological consequence. Biomarkers can serve different purposes across development, including measuring pathology, engagement, biological response, progression, or patient selection [19]. Their evidentiary value therefore depends on context of use rather than on the existence of a measurable change alone.

A useful pharmacodynamic readout should be responsive to intervention, interpretable in relation to the proposed mechanism, and measured over a time window capable of distinguishing transient perturbation from sustained biological change. Regulatory experience with PD biomarkers in biosimilar development demonstrates the importance of pharmacological sensitivity and fitness for the specific decision being made [20]. That regulatory context cannot simply be transferred to novel-drug efficacy, but the underlying distinction remains useful: analytical sensitivity, mechanistic proximity, and clinical relevance are different properties.

Randomized studies of PCSK9 inhibitors further demonstrate that pharmacodynamic responses can be characterized under controlled clinical conditions [21]. Such data can establish a reproducible downstream biological effect without establishing that the same readout represents the disease-modifying step required for clinical benefit.

The falsification logic is therefore again asymmetric. Failure of the predicted PD response after adequate exposure and convincing engagement challenges pathway propagation, the biomarker interpretation, or the assumed mechanistic chain. Presence of the response establishes only the link that was actually measured. Timing adds another dimension: an early proximal signal may disappear before a distal consequence develops, whereas persistent proximal modulation may coexist with absent downstream biology.

Because such temporal states can look similarly “positive” when reduced to a single biomarker time point, **Table 1** separates their mechanistic implications and the development questions that remain open.

Table 1. Temporal Pharmacodynamic States That Change the Interpretation of Early-Development Evidence

State and entry conditions		Evidence through time	Transition and reassessment
early-development state / Target engagement	Entry condition / Exposure support	Pharmacodynamic readout over time /	Delayed consequence still unresolved / Time-dependent validation need / Early-development consequence

Dependency on prior evidence			
Proposed early-development state: Exposure-incomplete Target engagement: Negative or uninterpretable	Entry condition: PD sampling occurs before site-relevant exposure is sufficiently established Exposure support: Incomplete or uncertain	Pharmacodynamic readout over time: Absent or noisy Dependency on prior evidence: Exposure prerequisite unmet	Delayed consequence still unresolved: Whether engagement is achievable Time-dependent validation need: Re-establish exposure during the biologically relevant window Early-development consequence: Revise delivery, dose, schedule, or exposure interpretation before judging the target
Proposed early-development state: Engagement-failure Target engagement: Absent	Entry condition: Informative exposure and a fit-for-purpose engagement measurement are available Exposure support: Adequate for interpretation	Pharmacodynamic readout over time: Downstream PD absent or uninterpretable Dependency on prior evidence: Exposure condition satisfied	Delayed consequence still unresolved: Whether failure is molecule- or target-specific Time-dependent validation need: Confirm the result across an informative exposure window and exclude measurement failure Early-development consequence: Challenge the molecule-target claim; continuation requires a credible testable alternative
Proposed early-development state: Engagement-positive/PD-negative Target engagement: Present	Entry condition: Engagement is demonstrated under interpretable exposure Exposure support: Adequate	Pharmacodynamic readout over time: Predicted downstream response absent Dependency on prior evidence: Exposure and engagement supported	Delayed consequence still unresolved: Pathway sufficiency, biomarker validity, or compensation Time-dependent validation need: Sample across the expected propagation window and use orthogonal downstream measures Early-development consequence: Interrogate pathway and biomarker assumptions rather than escalating solely to increase already demonstrated engagement
Proposed early-development state: Transient-PD Target engagement: Present	Entry condition: Engagement and an early PD response occur Exposure support: Adequate	Pharmacodynamic readout over time: Response appears then wanes or becomes temporally discordant Dependency on prior evidence: Earlier links supported	Delayed consequence still unresolved: Whether duration is sufficient for disease biology Time-dependent validation need: Align exposure, engagement, and distal PD trajectories over repeated dosing Early-development consequence: Reconsider schedule or required duration before assigning mechanistic failure
Proposed early-development state: Sustained-PD/clinical relevance unresolved Target engagement: Present	Entry condition: Engagement and predicted PD persist Exposure support: Adequate	Pharmacodynamic readout over time: Sustained or reproducible Dependency on prior evidence: Earlier mechanistic links supported	Delayed consequence still unresolved: Whether perturbed biology is clinically consequential Time-dependent validation need: Extend observation toward disease-relevant biological or clinical outcomes Early-development consequence: Treat the mechanism as biologically active while retaining the therapeutic hypothesis as unresolved

Patient and disease context

Even a coherent exposure–engagement–PD sequence is not context free. Biomarker interpretation can vary with disease stage, biological subtype, baseline pathway activity, prior treatment, and the extent to which the measured process is rate limiting in the treated population. Biomarker strategy in neuropsychiatric development, for

example, has been argued to require alignment with the biological dysfunction and phase-specific decision rather than reliance on diagnostic categories alone [22].

Quantitative systems pharmacology illustrates the same issue at a systems level. Translational behavior of bispecific T-cell engagers can depend on tumor burden, target abundance, immune-cell state, binding properties, and interactions among these variables. A QSP approach designed to reconcile experimental and clinical contexts demonstrates how the same nominal pharmacological intervention can behave differently as tumor and immune conditions change [23]. Such models do not capture every source of patient heterogeneity, but they show why context cannot simply be treated as a downstream nuisance after a mechanism has supposedly been confirmed.

The consequence for falsification is that a negative result should be localized to the biological conditions actually tested. If exposure is adequate, engagement occurs, and the expected PD response is present, absence of benefit may indicate that the perturbed pathway is insufficient in that disease state rather than that the drug failed pharmacologically. Conversely, absence of PD in one subgroup may reflect baseline pathway inactivity, compensatory circuitry, disease stage, concomitant treatment, or altered biomarker validity.

The proposed architecture therefore treats patient and disease context as part of the mechanistic claim itself. Programs should specify which biological conditions are expected to permit the mechanism to operate, which patient characteristics could alter the relationship between target modulation and downstream response, and which discordant findings would justify enrichment, redesign, or termination. Falsification is useful not because it terminates more programs, but because it makes continuation conditional on a remaining uncertainty that is explicit, localized, and testable.

Competing mechanistic explanations

The strongest use of falsification is not to convert every discordant result into program failure, but to narrow the set of explanations that remain plausible. LY3526318 provides a useful example. In healthy volunteers, the TRPA1 antagonist inhibited cinnamaldehyde-evoked dermal blood flow, supporting in-vivo human pharmacology [24]. Yet subsequent randomized studies in osteoarthritis pain, chronic low-back pain, and diabetic peripheral neuropathic pain did not show a statistically significant improvement in the prespecified primary pain outcome, and a hepatotoxicity signal further constrained development [25]. The combined evidence therefore does not support the inference that failure to improve pain arose from failure to engage TRPA1. It localizes the uncertainty downstream.

Several explanations remain compatible with such discordance. The engaged pathway may not be sufficiently causal in the tested disease state; the magnitude, duration, or anatomical location of modulation may be inadequate; compensatory biology may blunt the downstream consequence; the pharmacodynamic challenge may capture target activity without representing the relevant disease mechanism; or the clinical endpoint may be insensitive to the biological change that occurred. None of these alternatives should be invoked merely to preserve a preferred hypothesis. Each should generate a discriminating prediction that can itself be tested.

The proposed architecture therefore treats discordance as a branching point. Evidence should reduce the space of viable explanations. If a new experiment cannot distinguish among remaining explanations, its value for mechanistic continuation is limited even when it produces another favorable signal.

Pre-specified failure criteria

Failure criteria are most useful when they are specified before the result is known and when they identify which claim is at risk. A negative target-engagement result under uncertain tissue exposure should trigger a different decision from a negative result obtained at verified site exposure with a sensitive assay. Likewise, a pharmacodynamic failure after convincing engagement differs from an efficacy failure after sustained engagement and downstream biological response.

The criteria need not be rigid numerical cutoffs when the evidence does not justify them. They can instead define qualitative states: insufficiently informative, mechanism-inconsistent, compatible with an alternative explanation, or sufficiently concordant to justify the next test. What matters is that the program states prospectively what evidence would challenge exposure adequacy, molecule-target activity, pathway propagation, context dependence, or therapeutic relevance.

Residual uncertainty about dose at regulatory review illustrates why progression through development cannot itself be taken as evidence that dose has been optimized. In a retrospective analysis of 218 FDA-approved new molecular entities, dose modification or additional postmarketing dose assessment was identified for a subset of products, with downward changes predominating [26]. This does not show that a falsification-centred strategy

would have prevented those revisions, but it demonstrates that unresolved dose questions can survive late into development.

A falsification-centred early development architecture

The proposed architecture links four questions without collapsing them into a single success narrative: Was informative exposure achieved? Was the intended target engaged? Did engagement produce the predicted pharmacodynamic consequence? Did that consequence remain meaningful in the relevant patient and disease context? Each affirmative answer permits the next claim to be tested; it does not validate claims further downstream.

The framework also requires explicit return paths. If engagement is absent, the program should revisit exposure, delivery, assay validity, and molecule-target assumptions. If engagement is present but pharmacodynamics are absent, pathway sufficiency, timing, biomarker validity, and compensatory biology become higher-priority explanations. If engagement and pharmacodynamics are present without clinical consequence, disease dependence, patient selection, endpoint sensitivity, duration, and competing mechanisms move to the foreground. This structure is compatible with quantitative clinical pharmacology rather than opposed to it. Model-informed approaches to T-cell engager dosing show how exposure, safety, and pharmacology can be updated iteratively across starting-dose, step-up, and maintenance decisions [27]. Datopotamab deruxtecan provides a different example: integrated pharmacokinetic, efficacy, and safety analyses supported late-stage selection of a dose below the maximum tolerated dose [28]. Such cases do not validate the proposed falsification architecture, but they demonstrate that development decisions can change when evidence streams are considered jointly rather than ranked by a single milestone.

Decision consequences for dose escalation and continuation

Under a falsification-centred strategy, dose escalation is not automatically the response to weak downstream activity. More exposure is rational only when insufficient exposure remains a credible explanation and when safety permits the hypothesis to be tested more strongly. Escalating after target engagement is already saturated, or after a downstream mechanism has failed under informative conditions, can increase toxicity without resolving the relevant uncertainty.

Continuation should therefore depend on whether discordant evidence leaves a credible, testable alternative explanation. A program may continue after a failed link when a revised dose, schedule, formulation, biomarker, or patient-selection strategy can discriminate that explanation. Conversely, repeated positive proximal signals should not justify continuation indefinitely when the disease-relevant claim remains unsupported.

Modern oncology dose optimization increasingly reflects this logic. Multi-stakeholder work has emphasized biological activity, exposure-response, tolerability, delayed toxicity, and patient experience rather than automatic pursuit of the maximum tolerated dose [29]. The proposed framework extends that principle upstream: the purpose of dose escalation is to interrogate a mechanistic uncertainty, not simply to produce a higher exposure or another positive readout.

CONCLUSION

Early clinical development can be designed so that evidence does more than accumulate confidence. By decomposing a therapeutic hypothesis into exposure, target engagement, pharmacodynamic propagation, and context-dependent clinical relevance, programs can identify which claim has survived testing and which has failed or remains unresolved. Positive evidence then becomes conditional rather than cumulative, while discordant evidence becomes useful for localizing uncertainty.

The proposed falsification-centred architecture is not a validated algorithm and does not replace clinical judgment, quantitative modeling, safety governance, regulatory interaction, or therapeutic-area expertise. Its contribution is narrower: to make mechanistic assumptions explicit, require informative opportunities for them to fail, and connect continuation or escalation to the uncertainty that remains. Early development becomes more informative when the question is not simply whether another encouraging signal has appeared, but which explanation is still defensible after the evidence has had a genuine chance to contradict it.

ACKNOWLEDGMENTS: None

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

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