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A Risk-Based, Weight-of-Evidence Approach to Nonclinical Safety Assessment for First-in-Human Oncology Drug Development

White Paper | 2026

Executive Summary

Nonclinical safety assessments supporting first-in-human (FIH) oncology drug development should generate sufficient evidence to characterize safety risks, inform dose selection, and support appropriate clinical monitoring and risk mitigation. While *in vivo* studies have historically contributed to nonclinical safety assessments, the evidence needed to support these objectives may vary based on the investigational product, target biology, clinical context, relevance of available nonclinical models, and prior knowledge.

Current guidance provides flexibility to support a streamlined nonclinical safety strategy when scientifically justified. However, sponsors may face uncertainty regarding when a streamlined strategy is appropriate, and what evidence is sufficient to support it. This uncertainty may lead to additional or duplicative studies, even when their expected contribution to the human risk assessment is limited, potentially increasing development costs and timelines and delaying patient access.

To address these challenges, Friends of Cancer Research convened a multi-stakeholder working group including experts from patient advocacy organizations, pharmaceutical companies, academia, the Frederick National Laboratory for Cancer Research, and the U.S. Food and Drug Administration (FDA) to develop a practical approach for applying risk-based flexibility to nonclinical safety strategies supporting FIH oncology studies. The group developed a four-step framework and identified several key principles for its application:

- Assess scientific and clinical factors collectively: Scientific and clinical factors should be considered together to characterize what is known and where uncertainty remains. No individual factor, including the availability or absence of a pharmacologically relevant species, should independently determine whether a streamlined strategy is appropriate or which strategy should be pursued. As new evidence becomes available, the assessment should be revisited as appropriate.
- Focus on the expected value of additional evidence: Evidence generation should be directed toward specific uncertainties and the information needed to address them. Sponsors should consider what meaningful information an otherwise expected study would add to the human risk assessment and whether it would reduce remaining uncertainty. When a streamlined strategy is being considered, a weight of evidence (WoE) assessment should evaluate whether the available evidence is sufficiently relevant, reliable, and informative to justify the proposed approach and identify what uncertainty remains. In some cases, existing evidence may sufficiently address the relevant uncertainties, such that additional evidence generation would provide limited incremental value.
- Ensure the resulting strategy remains sufficient to support FIH development: Sponsors should describe how the available evidence adequately supports human risk assessment, including (1) characterization of potential safety risks to inform clinical monitoring and (2) selection of the starting dose and initial dose-escalation decisions. Remaining uncertainty should be clearly communicated in regulatory interactions and submissions to support patient safety.

The proposed framework provides a structured approach for integrating product-specific scientific factors, clinical context, applicable guidance, and the totality of available evidence to determine when a streamlined nonclinical strategy may be scientifically justified, and how it should be applied. A risk-based approach does not lower the evidentiary standard needed to support FIH clinical development; rather, it focuses evidence generation on studies and approaches that meaningfully address remaining uncertainty. Successful use of the framework will require collaboration among sponsors, regulators, researchers, patient advocates, and other stakeholders, supported by greater sharing of experience and learning from its application in practice.

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We thank the working group members for their expertise and contributions that helped shape the development of this white paper. The views expressed here represent the collective insights from working group discussions and do not necessarily reflect the official positions of any individual organization.

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Introduction

Nonclinical safety assessment plays a central role in oncology drug development. It includes supporting the Investigational New Drug (IND) application and the initiation of clinical testing while helping to characterize potential toxicities, inform starting dose and initial dose-escalation strategies, guide clinical monitoring and risk mitigation, and shape additional safety assessments as development progresses. Historically, nonclinical safety assessments have relied substantially on *in vivo* animal studies, although nonclinical evidence may be generated through a broader range of approaches. In some settings, however, animal studies may provide limited or redundant insight when available models lack sufficient relevance or other evidence already adequately informs clinical risk.

Current expectations for nonclinical safety strategies supporting oncology drug development are primarily established in International Council for Harmonisation (ICH) guidance, particularly ICH S9 and the accompanying S9 Questions & Answers (Q&A) document.[1,2] For products within its scope, ICH S9 provides flexibility in the type, timing, and design of nonclinical studies based on the investigational product, clinical context, development stage, and modality, while protecting patients and avoiding unnecessary animal use consistent with the 3Rs principles (Replacement, Reduction, and Refinement). Recent U.S. Food and Drug Administration (FDA) guidance, including draft guidance on streamlined nonclinical safety studies for oncology biologics and conjugated products, reflects the use of integrated, risk-based evidence to support tailored nonclinical strategies when scientifically justified.[3–5] A *weight-of-evidence (WoE)*[1] assessment integrates the totality of relevant evidence to inform human safety risk assessment. Such an approach is already applied in other areas of nonclinical safety assessment, with the specific evidence considered depending on the purpose of the assessment, product characteristics, and development context.

Sponsors may nevertheless face uncertainty about when the scientific and clinical context support the use of a streamlined nonclinical strategy and what evidence is sufficient to justify that approach. In turn, sponsors may generate nonclinical evidence that does not meaningfully reduce uncertainty or improve human risk assessment, potentially extending development timelines and delaying patient access. Regional differences in regulatory expectations may further influence these decisions, particularly for global development programs (Box 1).

Friends of Cancer Research coordinated a working group of experts to develop recommendations to enable a more consistent and confident application of risk-based flexibility in nonclinical safety assessment across oncology therapeutics. This white paper focuses on nonclinical safety evidence supporting first-in-human (FIH) oncology studies, while recognizing that some principles may also be relevant later in development. The goal is to identify the underlying scientific considerations that should inform the appropriate nonclinical strategy for a given product and clinical context, rather than treat examples as categorical exceptions or limit flexibility to product classes explicitly described in existing guidance. We propose a practical, decision-oriented framework to help sponsors determine when a streamlined nonclinical strategy is scientifically justified, evaluate the supporting evidence through a WoE framework, and communicate the rationale and

[1] *Weight of Evidence (WoE).* An integrated scientific assessment of the totality of relevant evidence to inform human risk assessment. The assessment should consider only quality and reliable data, critically evaluating the remaining uncertainty. A strong WoE assessment may provide the basis for streamlined nonclinical strategies.

remaining uncertainty in a consistent manner. The framework is intended to guide scientific judgment rather than to be prescriptive based on any individual factor.

This white paper is one of three complementary Friends of Cancer Research publications exploring opportunities to modernize early-phase oncology drug development through more efficient, evidence-based approaches that maintain patient safety.[6,7]

Box 1. Regulatory Insights on Applying Current Nonclinical Guidance in Oncology

Current FDA and ICH guidance documents provide a foundation for nonclinical safety planning, but their application in oncology is context dependent. For oncology indications, FDA review divisions may generally begin with ICH S9 and the accompanying S9 Q&A rather than defaulting to ICH M3(R2), while ICH S6(R1) may also inform the assessment of biotechnology-derived products.[1,2,8,9] Streamlined approaches may be considered when scientifically justified based on the investigational product and clinical context. This flexibility is not limited to reducing or streamlining studies; expectations may be adapted where scientifically justified, and ICH S9 concepts may inform approaches for certain indications beyond advanced cancer when the underlying clinical and safety considerations are similar.

Sponsors developing global programs also need to consider differences across regulatory regions. While FDA oncology guidance may provide additional flexibility beyond that described in ICH S9 and the S9 Q&A, sponsors may continue to follow ICH-based or other regional expectations to support development across multiple geographies. As a result, sponsors may plan or conduct additional studies to de-risk global development, even when those studies are not needed to support the initial U.S. IND. Separately, nonclinical evidence needs may evolve as treatment duration, patient population, or stage of development changes, which may warrant additional studies later in development.

These considerations underscore the importance of distinguishing among evidence generated to (1) support human risk assessment and patient safety, (2) meet expectations under current guidance or regional practice, and (3) support global development, later-stage trials, or marketing applications.

Current Nonclinical Safety Expectations and Opportunities for Flexibility in Oncology Drug Development

To support FIH oncology drug development, the data package may include repeat-dose toxicity studies in one or more animal species, depending on the modality, *pharmacologic relevance*[2], and applicable guidance. A streamlined nonclinical strategy may be considered when there is:

- **Lack of pharmacologically relevant species.** When an investigational product does not bind the intended target or elicit relevant pharmacologic activity in an available animal species, *in vivo* toxicology studies in that species may not meaningfully inform on-target human safety risk and may be difficult to interpret. In such circumstances, other nonclinical evidence may be needed to characterize risk.

[2] *Pharmacologic relevance.* The extent to which a nonclinical species or model reflects the anticipated pharmacologic activity of the investigational product. Pharmacologic relevance may be informed by factors such as target expression and distribution, target binding and functional activity, achievable exposure, demonstrable pharmacodynamic response, and species-specific biology.

- Partial or limited evidence of pharmacologic or biological relevance. Additional characterization may be needed to determine whether an available animal model is sufficiently relevant and informative to support the safety assessment.
- Existing product, target, class, platform, modality, or clinical experience that already informs anticipated safety risks. This may be particularly relevant for well-characterized and/or clinically validated targets or modalities. The extent to which such evidence can support a streamlined strategy will depend on its relevance, robustness, and applicability to the investigational product, as well as whether important safety uncertainties remain. Where existing evidence sufficiently informs the human risk assessment, animal studies may provide limited additional value.

Prior experience supports human risk assessment only to the extent that it is relevant, high quality, applicable, and available. Product-specific differences, evidence gaps, or limited access to relevant data can weaken that support and may warrant additional nonclinical evidence.

Assessing pharmacologic relevance can require considerable scientific judgment, particularly when the available evidence is informative, but uncertainty remains about how well the nonclinical model reflects human pharmacology. For instance, target expression, binding and functional activity, achievable exposure, pharmacodynamic response, and species-specific biology may provide different answers about how well an animal model reflects human pharmacology. Sponsors and regulators may therefore reach different conclusions regarding whether the observed degree of relevance is sufficient to inform the safety assessment or whether it warrants further characterization.

Importantly, the availability of a pharmacologically relevant species does not, by itself, determine the value of a particular animal study. The relevance of an animal model also depends on the assessment purpose. For example, a model with limited target-based pharmacologic relevance may still provide information relevant to off-target toxicity for certain modalities. In some cases, sponsors may generate *in vivo* data from exploratory or non-Good Laboratory Practice (GLP) compliant studies to further characterize relevance and inform whether an otherwise expected GLP toxicology study would provide meaningful additional information for human risk assessment.

This presents a practical challenge: sponsors need to determine when the totality of available evidence provides sufficient scientific justification to consider a streamlined nonclinical strategy. The proposed framework is intended to make this assessment more explicit by connecting the scientific and clinical characteristics of the investigational product and its intended use, otherwise expected approach, supporting available evidence, residual uncertainty, and patient-safety measures to support clear scientific justification and regulatory communication.

Structured Approach to Developing a Risk-Based Nonclinical Safety Strategy

A risk-based approach does not mean reducing the amount of evidence available to characterize the safety profile of an investigational product. Rather, the extent, timing, source, and relevance of evidence should be tailored to the investigational product, the proposed clinical context, and the uncertainty in the available evidence. The central question is whether the totality of evidence sufficiently supports the human risk assessment, and whether additional studies would provide meaningful new or supporting information.

This approach focuses on nonclinical safety assessments supporting FIH oncology studies and is not intended to prescribe a single nonclinical package or serve as a full lifecycle development model. In oncology, FIH studies are generally conducted in patients rather than healthy volunteers, which changes the

benefit-risk considerations. Therefore, the patient population, disease severity, unmet need, and ability to detect, monitor, or manage anticipated toxicities may influence the nonclinical safety assessment and the significance of remaining uncertainty before clinical testing.

The proposed approach distinguishes two related components of risk-based decision-making.

- First, a structured risk-based decision framework considers whether the scientific and clinical characteristics of the investigational product provide a basis to consider a nonclinical strategy that differs from the otherwise expected approach.
- If a streamlined nonclinical strategy is considered, a subsequent WoE assessment evaluates whether the available nonclinical evidence is sufficiently relevant, reliable, and informative to support the human risk assessment and justify that strategy.

The four-step approach operationalizes this sequence. Steps 1 and 2 characterize relevant scientific and clinical considerations and determine whether there is a basis to consider a streamlined strategy. Step 3 applies the WoE assessment when a streamlined nonclinical strategy is considered, and Step 4 defines the resulting nonclinical strategy and how remaining uncertainty will be managed. The process may be iterative, as additional evidence generated to address uncertainty may change the initial assessment and the appropriate nonclinical strategy. Figure 1 summarizes this overall decision process, including the relationship between scientific characterization, the WoE assessment, and the resulting nonclinical strategy.

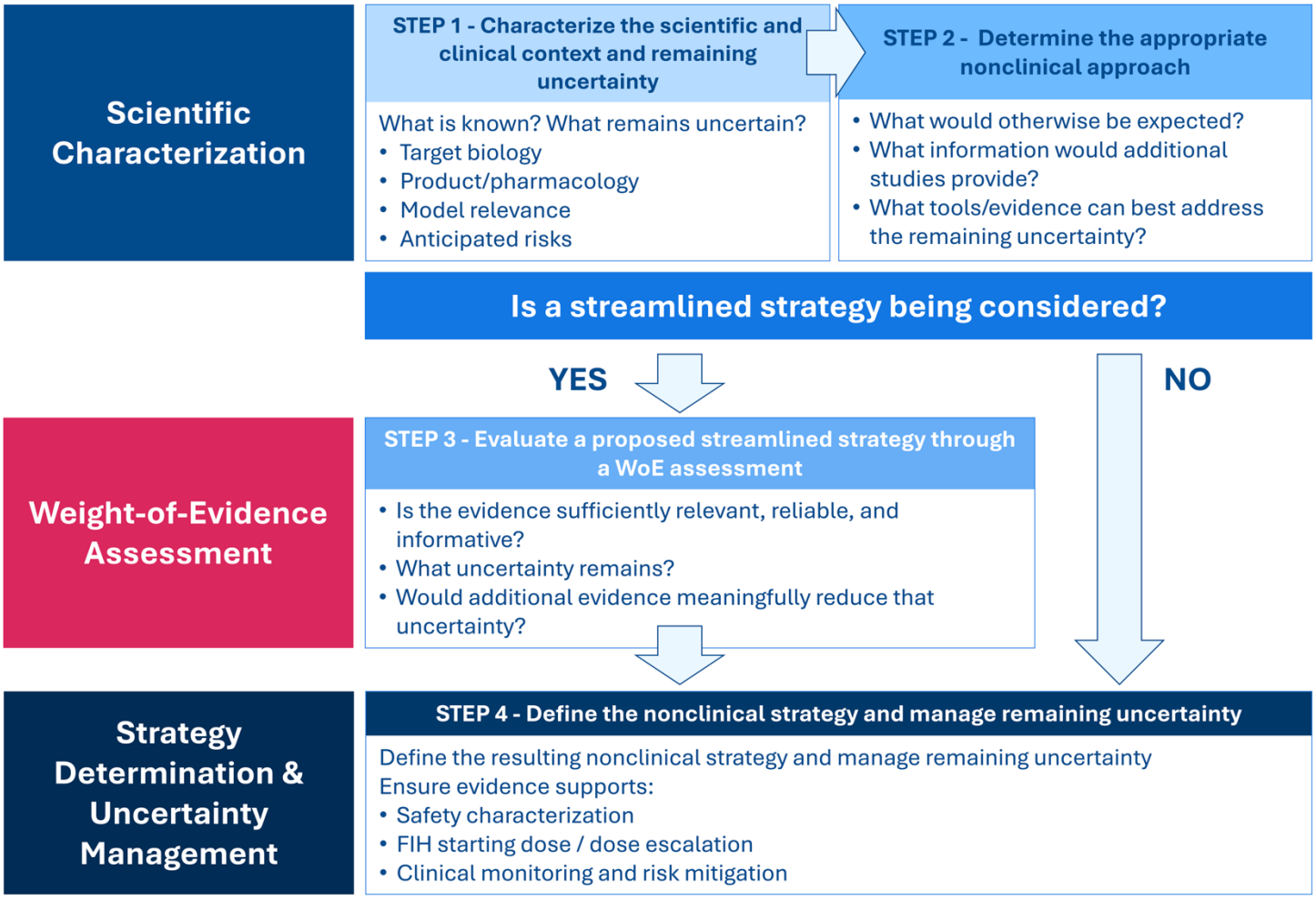

Figure 1. Framework for developing a risk-based nonclinical safety strategy to support FIH oncology development.

Step 1. What does the product-specific scientific assessment indicate?

Relevant scientific factors should be assessed, including the molecular target and target biology, product modality and pharmacologic characteristics, the relevance of available nonclinical models, anticipated safety risks, and clinical context, to determine what is known and what remains uncertain.

Figure 2 summarizes high-level scientific factors that inform whether there is a basis to consider a streamlined nonclinical strategy and illustrates how each may range from circumstances providing less support to those providing greater support for considering a streamlined nonclinical strategy. Appendix Table A1 provides the corresponding subcategories and questions sponsors may consider when characterizing each factor. These considerations are intended to be evaluated collectively rather than as independent criterion with fixed thresholds. The relative importance of each factor will depend on the product and clinical context, and no individual factor should automatically determine whether a streamlined strategy is appropriate, or which strategy should be pursued.

The assessment of some factors may change as additional evidence is generated, while others, such as disease severity, patient population, or treatment setting, are inherent to the clinical context. The absence of a pharmacologically relevant species may provide a clear scientific basis for considering a streamlined approach because an otherwise expected animal study may not meaningfully inform the human risk assessment. Conversely, when a relevant species is available, its availability alone should not determine whether a particular in vivo study is needed. Sponsors should consider whether the study would meaningfully address an identified uncertainty and what information it would add in the context of the other available evidence.

Step 2. What nonclinical approach is appropriate based on the scientific assessment and applicable guidance?

Sponsors should establish what would ordinarily be expected under applicable guidance, then consider whether the initial product-specific assessment (Step 1) provides a scientific basis for a different approach. They should assess whether the otherwise expected studies would provide meaningful additional information for the human risk assessment and consider which available approaches are best suited to address the identified uncertainties. If proposing a streamlined strategy, sponsors should describe the proposed approach and articulate its scientific rationale.

As additional evidence is generated, sponsors may revisit the Step 1 assessment and refine the proposed strategy.

Step 3. If a streamlined strategy is considered, does the WoE justify that approach?

If Steps 1 and 2 support consideration of a streamlined nonclinical strategy, sponsors should conduct a WoE assessment to determine whether the evidence is sufficient to justify the proposed strategy, what uncertainty remains, and whether additional evidence would meaningfully reduce that uncertainty.

TARGET, PRODUCT & PHARMACOLOGY		
Novel or poorly characterized modality or molecular characteristics	Modality and molecular characteristics	Established and well-characterized modality and molecular characteristics
Limited understanding of target expression, biology, or normal function	Target knowledge	Target biology / function is well characterized / clinically validated, including expression in relevant tissues
Selectivity is difficult to establish or there is greater uncertainty regarding off-target activity	Selectivity and off-target pharmacology	Selectivity is well characterized and/or available evidence indicates a low likelihood of clinically relevant off-target activity
NONCLINICAL MODELS		
Available species is pharmacologically relevant and informative for the intended assessment	Pharmacologic relevance of available species	No pharmacologically relevant species is available, or available species have limited relevance for the intended assessment
RISK CHARACTERIZATION		
Potential risks are poorly understood, complex, or difficult to characterize	Nature and predictability of potential risks	Potential risks and their drivers are relatively well understood and predictable
CLINICAL CONTEXT		
Lower disease severity and/or lower unmet need, with effective treatment options available	Patient population, unmet need, and disease severity	Severe or life-threatening disease and/or high unmet need, including settings where available treatment options have limited effectiveness
Anticipated risks may be difficult to monitor or manage and may require further characterization	Clinical monitoring and manageability	Anticipated risks can be appropriately monitored, mitigated, or managed clinically

Figure 2. Scientific and Clinical Factors Informing Consideration of a Streamlined Nonclinical Strategy

Evaluating Evidence Through a WoE Assessment

Through a WoE assessment, sponsors should evaluate whether the available evidence is sufficiently relevant, reliable, and informative to support the proposed strategy. Evidence may come from existing knowledge and experience or prospectively generated data, with the appropriate evidence depending on the investigational product, proposed strategy, and remaining uncertainty. Table 1 summarizes illustrative evidence sources and the roles they may play in the WoE assessment, including prior human experience, in vivo data, *new approach methodologies (NAMs)*[3] and other human-relevant models, and quantitative or computational approaches.

In some circumstances, existing evidence may sufficiently address the relevant uncertainties without additional data generation. In others, additional evidence may be needed to address a specific gap or support modification or replacement of an otherwise expected study.

Considerations may include:

- Relevance and applicability: Evidence that more directly reflects the investigational product, target, mechanism, modality, clinical context, or safety question should generally provide stronger support than evidence requiring substantial extrapolation.
- Source and prior experience: Evidence may come from internal data, publications, or other external sources. Publication or peer review should not automatically confer greater confidence; relevant internal data may be informative, particularly when supported by experience across related products, classes, or platforms. Prior regulatory use of the same or a similar evidence source, model, or approach may further increase confidence in its applicability.
- Contribution of prospectively generated in vivo evidence: Prospective in vivo studies are one potential way to address remaining uncertainty. The species, exposure, duration, study design, and use of GLP or non-GLP methods should be selected based on the purpose of the study and the information it is expected to add to human risk assessment.
- Robustness and intended use of NAM-derived evidence: Evidence generated using NAMs should be considered based on the technical characterization and reliability of the method, its biological relevance and applicability to the investigational product, and its intended use. The level of characterization should be commensurate with the role the NAM-derived evidence is intended to play in the WoE assessment, whether to complement other evidence, address a specific gap, or support modification or replacement of an otherwise expected study. A NAM does not necessarily need to be fully validated to contribute to a WoE assessment; fit-for-purpose NAMs may be considered based on their intended context of use and the toxicological question being addressed.[10]

The evidence sources summarized in Table 1 are not intended to establish a fixed hierarchy or prescriptive weighting scheme. The contribution of each evidence source should depend on its ability to address the uncertainty being evaluated. Once the WoE assessment and proposed streamlined strategy have been

[3] *New Approach Methodologies (NAMs).* Methods and technologies used to generate information relevant to nonclinical safety, pharmacology, and pharmacokinetic assessments that provide an alternative to conventional animal studies, including *in vitro*, *ex vivo*, in chemico, in silico, microphysiological systems, organ-on-chip, and other human-relevant alternative methods. Depending on their intended context of use, NAMs may complement, reduce, refine, or in some circumstances replace conventional *in vivo* studies.

developed, engagement with the FDA and, as relevant, other regulatory authorities, is recommended to discuss the scientific rationale, supporting evidence, remaining uncertainties, and whether additional evidence is needed.

Table 1. Evidence Sources and Their Role in the WoE Assessment.

Evidence category	Evidence source / approach	Role in the WoE assessment
Prior human and related product experience	Clinical data from the investigational product or products with a relevant target, mechanism, modality, class, or platform	Informs anticipated safety risks and clinical manageability when sufficiently applicable to the investigational product and clinical context
In vivo evidence	Animal studies, such as general toxicology, exploratory/non-GLP, and mechanistic or pharmacology studies, including transgenic or humanized models where relevant	Characterizes toxicity, exposure–toxicity relationships, target-organ effects, or model relevance depending on pharmacologic relevance, exposure, species biology, and study design. Specialized or modified models may also provide human-relevant functional or pharmacodynamic information when appropriately characterized
NAMs and other human-relevant models	In vitro and *ex vivo* approaches: Mechanistic and pharmacologic approaches, including target binding, pathway modulation, receptor occupancy, and relative potency assessments	Supports characterization of target engagement, mechanism-related risks, selectivity, off-target effects, relative potency, and biological plausibility
	Targeted hazard approaches: Assays directed at a specific anticipated toxicity, such as cytokine-release assays or other immune-function assays, gastrointestinal or bone marrow toxicity	Addresses a specific potential toxicity when the assay is biologically relevant and informative for the anticipated human risk
	In silico and quantitative approaches: including PBPK, PK/PD, exposure-response, QSP, computational toxicology, and drug-drug interaction modeling	Supports assessment of exposure, pharmacology, dose selection, drug-drug interactions, or translation across systems, depending on model assumptions, input data, and intended use

Abbreviations: GLP, Good Laboratory Practice; NAMs, new approach methodologies; PBPK, physiologically based pharmacokinetic; PK/PD, pharmacokinetic/pharmacodynamic; QSP, quantitative systems pharmacology

Step 4. What nonclinical strategy should be pursued, and how will remaining uncertainty be managed?

Based on the preceding scientific assessment and, when applicable, WoE assessment, sponsors should determine the appropriate nonclinical strategy. This may involve proceeding with the otherwise expected approach or pursuing a streamlined strategy that modifies, reduces, replaces, defers, or omits otherwise expected nonclinical studies, including animal studies. For a strategy supporting FIH clinical development, sponsors should describe how the available evidence adequately supports human risk assessment,

including (1) characterization of potential safety risks to inform clinical monitoring and risk mitigation and (2) selection of the starting dose and initial dose-escalation strategy.

Sponsors should identify any remaining uncertainty and describe how additional evidence or clinical risk-mitigation measures will address that uncertainty. The resulting nonclinical strategy, supporting WoE, when applicable, and approach to managing the remaining uncertainty should be clearly communicated in regulatory interactions and submissions, including the scientific rationale supporting why the selected strategy is appropriate for the investigational product and clinical context. How a scientifically justified strategy is pursued may also be influenced by regulatory considerations and the feasibility of conducting studies, which should be distinguished from the residual safety uncertainty identified through the scientific assessment and, when applicable, WoE assessment (Box 2).

Box 2. Regulatory and Implementation Considerations for Risk-Based Nonclinical Strategies

A scientifically justified streamlined nonclinical strategy may still carry uncertainty regarding regulatory acceptance, particularly when it departs from guidance-based expectations, relies on less familiar evidence sources, or involves areas where scientific judgment may differ. Early regulatory engagement can help sponsors discuss the proposed evidence, remaining safety uncertainty, and rationale for the streamlined strategy before implementation.

Sponsors may also face implementation challenges because mechanisms for obtaining regulatory feedback on novel nonclinical approaches, including NAMs, are not always clear or consistent across regulatory authorities. Engagement may be valuable both within a product-specific development program and earlier in the development of a NAM or supporting data package, where feedback can help establish confidence that the approach is fit-for-purpose for a specified context of use. Greater clarity and predictability around these engagement pathways could facilitate the use of scientifically justified streamlined strategies. Differences across regulatory authorities, limited public precedent, right-of-reference limitations when relying on prior knowledge, and varying levels of familiarity or confidence within sponsor and clinical teams may influence whether and how a streamlined strategy is pursued.

These considerations underscore the importance of distinguishing between residual safety uncertainty and regulatory or implementation uncertainty. Residual safety uncertainty identified through the WoE assessment should inform clinical decisions such as starting dose, dose escalation, eligibility criteria, monitoring, and other patient-protection measures. Regulatory or implementation uncertainty should be addressed through early engagement, clear scientific justification, and development planning, rather than treated as evidence of greater safety risk or automatically driving additional nonclinical studies or more conservative clinical decisions.

Illustrative Case Studies

Risk-based nonclinical strategies will depend on the investigational product, existing knowledge, available models, and the specific uncertainties that need to be addressed. The following examples illustrate how the framework applies in different decision contexts.

Integrating the totality of evidence when *in vivo* models have limited relevance

Bispecific antibodies may present particular challenges for nonclinical safety assessment when available animal models do not fully reflect the pharmacology of the investigational product. In one published, anonymized case, a bispecific antibody developed for solid tumors targeted two clinically validated immune-

checkpoint pathways, but one binder did not bind non-human primates (NHPs), limiting the ability of the NHP model to characterize the pharmacology of the full investigational product.[11] Although the expected nonclinical package in support of a phase 1 trial under ICH S9 would generally include a 1-month repeat-dose toxicity study, this limitation of the available model raised the question of whether such a study would meaningfully inform human risk assessment and what other evidence could address the remaining safety uncertainties.

The sponsor therefore assembled a WoE package drawing on multiple sources of evidence. This included comprehensive *in vitro* characterization of the investigational product's potency, efficacy, specificity, and selectivity; a 16-day NHP toxicity study using a cross-reactive precursor molecule; and a review of *in vivo* nonclinical safety data from three related bispecific molecules directed against the same target pair. The sponsor also incorporated published information on the individual targets and proposed using the precursor molecule for pharmacokinetic (PK) modeling of clinical candidate exposure and receptor occupancy, supported by available clinical PK data from molecules directed against the individual targets. Together, these data were used to characterize the anticipated safety profile and support FIH dose selection without conducting an additional repeat-dose *in vivo* safety study with the clinical candidate.

The FDA agreed that a repeat-dose toxicity study was not needed, provided that the IND included the supportive pharmacology data and information characterizing the limitations of available rodent and nonrodent species for assessing the investigational product. The FDA also considered the proposed WoE approach reasonable and recommended that it include a literature-based assessment of potential toxicities associated with both targets, details and assumptions underlying any modeling used for FIH dose selection, and available direct comparative pharmacology when clinical data from related constructs were used.

Key Insight: When available models may provide limited information, the decision to conduct or omit an otherwise expected study should be based on the specific uncertainties that remain and the information the study is expected to add. This case demonstrates that the reasoning captured by the proposed framework is already being applied in practice: remaining safety questions were identified, and multiple evidence sources were integrated to determine whether additional *in vivo* testing would meaningfully improve the human risk assessment.

Leveraging prior knowledge in a next-in-class small molecule program

Consider a new small-molecule oncology drug directed against a clinically validated target for which multiple products in the same or a closely related mechanistic class have already been approved. Existing nonclinical and clinical experience may provide substantial information regarding target biology, anticipated on-target toxicities, exposure–response relationships, and approaches to clinical monitoring and risk mitigation. At the same time, the new molecule has its own selectivity profile, metabolites, exposure characteristics, and potential off-target pharmacology. Pharmacologically relevant rodent and nonrodent species are available, and initial product-specific pharmacology and exploratory *in vivo* findings are generally consistent with the established class profile.

In this setting, the availability of relevant species would not itself determine what evidence is necessary for the new program. The scientific assessment would distinguish uncertainties informed by prior target or class experience from those arising from the new molecule, where product-specific evidence would remain most important. The sponsor could evaluate the incremental contribution of otherwise expected repeat-dose studies or study elements. A WoE assessment could integrate prior human and class experience with product-specific pharmacology, in vitro selectivity and off-target characterization, metabolite coverage,

exposure, and exploratory *in vivo* findings. Concordance across these sources could support consideration of a streamlined approach, whereas molecule-specific differences, discordant findings, insufficient exposure, or a new safety signal would increase the value of additional product-specific evidence.

A streamlined strategy would therefore not be justified simply because other drugs against the same target have been developed. It would depend on demonstrating that prior knowledge is sufficiently applicable to the new molecule, identifying the uncertainties that remain product-specific, and showing that the proposed evidence addresses those uncertainties while still supporting characterization of potential safety risks and FIH starting-dose and dose-escalation decisions.

Key Insight: Prior knowledge can reduce uncertainty without replacing the need for product-specific evidence. The framework helps distinguish risks already informed by related products from uncertainties introduced by the new molecule, focusing evidence generation where it is most informative.

Conclusions and Future Directions

Risk-based nonclinical safety assessment should focus on generating the evidence needed to support human risk assessment, FIH dose selection, and patient safety rather than on completion of a predetermined nonclinical package. The framework proposed in this paper provides a structured approach for integrating product-specific scientific factors, clinical context, applicable guidance documents, and the totality of available evidence to determine when a streamlined nonclinical strategy may be scientifically justified. Importantly, streamlined strategies do not necessarily mean less evidence; they are intended to focus evidence generation on the studies and approaches that meaningfully address remaining uncertainty. By focusing nonclinical evidence generation on the questions most relevant to patient safety, this approach can support timely, evidence-based initiation of FIH oncology studies while maintaining appropriate safeguards for patients enrolling in these studies.

Applying these principles consistently will require continued experience and collaboration among sponsors, regulators, researchers, patient advocates, and other stakeholders. This framework is intended to complement broader efforts to modernize FIH oncology development by focusing specifically on the nonclinical evidence needed to support safe and scientifically justified initiation of clinical studies.[6]

Although this framework focuses on evidence supporting FIH development, similar principles may also be informative later in development when considering the incremental value of additional or longer-duration toxicology studies. Several areas warrant continued work:

- Increase regulatory clarity and public precedent for streamlined strategies. Greater transparency around when streamlined strategies have been considered acceptable, the evidence supporting those decisions, and circumstances in which additional evidence was requested could help sponsors better understand how risk-based principles can be applied in practice.
- Advance fit-for-purpose use of NAMs and other human-relevant models. Continued experience is needed to define how novel models can contribute to specific safety questions, what level of characterization is appropriate for their intended use, and how sponsors can engage regulators as these methods are developed and applied.
- Enable more effective use of prior knowledge. Existing human and nonclinical experience with related targets, mechanisms, products, classes, or platforms may inform a new program, but its use may be limited by data availability, proprietary information, and right-of-reference restrictions.

Greater sharing of nonconfidential experience and consideration of mechanisms that facilitate the use of relevant prior evidence could strengthen WoE assessments.

- Advance global regulatory alignment. Recognizing that regulatory requirements and development needs may differ across regions, greater convergence around the scientific principles supporting streamlined nonclinical strategies could reduce duplicative nonclinical studies.
- Evaluate applicability beyond oncology. Many of the principles underlying the framework may also be relevant to severely-debilitating or life-threatening diseases outside oncology. Further work involving experts from other therapeutic areas is needed to determine where these principles are transferable and how they should be adapted to different disease settings, patient populations, and regulatory contexts.

As experience with risk-based nonclinical strategies grows, continued sharing of examples and regulatory experience can help refine how these principles are applied in practice. The goal should remain a scientifically justified, fit-for-purpose nonclinical strategy in which the rationale for the selected approach is clearly articulated and evidence generation is directed toward the uncertainties that matter most for patients enrolling in clinical studies.

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Appendix

Table A1. Questions to Support Characterization of Scientific Considerations

Scientific Domain	Factor for Consideration	Questions for sponsors to consider
Target, Product and Pharmacology	Modality and molecular characteristics	• What is the modality or molecular format (e.g., small molecule, biologic, conjugated product), and how well is it characterized? • Are there product-specific characteristics, such as a payload, linker, fragment crystallizable (Fc) modification, multivalency, or other components, that could affect the anticipated safety profile? • How well is the mechanism of action understood?
	Target knowledge	• Where is the target expressed, including in relevant normal tissues? • What is known about its biological function? • What biological effects may result from target modulation? • How well characterized or clinically validated is the target based on relevant and available nonclinical and human evidence?
	Selectivity and off-target pharmacology	• How well characterized is the product's selectivity for the intended target relative to potential off-target interactions? • Are secondary or off-target pharmacologic effects anticipated? • How confident can those effects be identified and characterized?
Nonclinical models	Pharmacologic relevance of available species	• Is there a pharmacologically relevant species? • Can relevant exposure and pharmacologic activity be achieved? • Are there species-specific limitations that affect interpretation?
Risk characterization	Nature and predictability of potential risks	• What potential safety risks remain important to characterize? • How well understood are the biological drivers of those risks? • Are potential effects predictable based on the mechanism, target biology, product characteristics, or prior experience? • Are there features of the anticipated risks that may limit their characterization in available models?

Clinical context	Patient population, unmet need, and disease severity	• What is the intended FIH patient population and disease setting? • What effective treatment options are available? • What is the level of unmet medical need and disease severity, and how might the clinical setting influence the significance of remaining uncertainty?
	Clinical monitoring and manageability	• Can anticipated toxicities be detected or monitored clinically? • Are effective mitigation strategies available? • How readily could an emerging toxicity be managed through dosing, treatment interruption, supportive care, or other clinical measures? • Will the investigational product be administered in combination, and what is known about potential overlapping or additive toxicities with the combination partner(s)?