Safety Assessment

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Nonclinical Toxicology Considerations Supporting Oncology Drug First-in-Patient Regulatory Submissions

Experience-based insights from early-phase small molecule oncology programs

Nonclinical toxicology plays a critical role in enabling oncology drug regulatory agency submissions (e.g., Investigational New Drug [IND] or Clinical Trials Application [CTA]) by establishing an evidence-based foundation for first-in-patient dosing and clinical risk management. Unlike non-oncology programs, oncology development operates within a distinct regulatory framework that prioritizes patient benefit while acknowledging a higher tolerance for risk in serious and life-threatening disease.

This white paper draws from an evaluation of 60 small-molecule oncology drug candidates that advanced to first-in-patient clinical dosing. Across these programs, repeat-dose toxicity studies in rodent and non-rodent species identified predictable target organ findings, including lymphoid, gastrointestinal, bone marrow/hematologic, and liver effects. Importantly, these findings did not prevent clinical entry; instead, when properly characterized, they supported dose justification, investigator guidance, and clinical monitoring strategies.

Predictable toxicities do not delay regulatory submission when they are understood, contextualized, and proactively managed.

Oncology Toxicology is a Risk Management Discipline

The purpose of oncology toxicology testing is not to eliminate every signal of toxicity. It is to identify what is clinically relevant, understand how it relates to pharmacology or exposure, and translate those findings into a rational starting dose and patient monitoring plan. ICH S9 recognizes that oncology programs require a risk-benefit approach, especially when first-in-patient trials involve patients with advanced cancer.

- Support selection of a safe and rational clinical starting dose.
- Identify potential target organs and dose-limiting toxicities.
- Inform clinical monitoring, dose escalation, and investigator guidance.
- Help sponsors explain why observed toxicities are monitorable, manageable, and acceptable in context.

Client Implication: A strong oncology drug toxicology package is not defined by studies showing no evidence of toxicity. It is defined by a clear scientific explanation of what was observed, why it matters, and how it will be managed clinically.

What the 60-Program Dataset Shows

The reviewed dataset included 60 small-molecule oncology drug candidates supported by rodent and non-rodent Good Laboratory Practice (GLP) toxicity studies. The majority were orally dosed, with studies generally conducted over four weeks and preceded by dose range-finding studies. The analysis focused on target organ findings identified through histopathology, along with selected clinical observations, hematology changes, and electrocardiogram or heart rate changes, where relevant.

Table 1. Target organ findings observed across 60 small-molecule oncology candidates.

Body System	Rodent Findings	Non-Rodent Findings	Interpretive Relevance for IND Planning
Lymphoid	42/60 (70%)	34/60 (57%)	The most frequent system affected both species. Common findings included lymphoid depletion or decreased cellularity.
Gastrointestinal	26/60 (43%)	23/60 (38%)	Frequently involved stomach or intestine ulceration, erosion, inflammation, atrophy, necrosis, or abnormal feces/emesis.
Bone marrow/ hematologic	25/60 (42%); hematology changes 49/60 (82%)	22/60 (37%); hematology changes 42/60 (70%)	Findings included hypocellularity or decreased cellularity, with broader hematology changes.
Liver	25/60 (42%)	16/60 (27%)	Common findings included hepatocellular necrosis, degeneration, inflammatory infiltrates, extramedullary hematopoiesis, pigment, or hypertrophy.
Kidney	15/60 (25%)	11/60 (18%)	Common findings included tubular degeneration, necrosis, regeneration, dilatation, basophilia, or interstitial nephritis.
Male reproductive organs	16/60 (27%)	12/60 (20%)	Findings included testicular tubular degeneration or necrosis, epididymal oligospermia, and related changes.
Female reproductive organs	20/60 (33%)	3/60 (5%)	Findings were more common in rodents and included ovarian, uterine, vaginal, or cervical changes.
Endocrine	18/60 (30%)	5/60 (8%)	Included adrenal, pituitary, thyroid, or parathyroid findings.
Bone	17/60 (28%)	5/60 (8%)	Findings included growth plate dysplasia, epiphyseal thickening, or altered spongiosa.
Skin	14/60 (23%)	2/60 (3%)	Included ulceration, erosion, inflammation, hyperplasia, hypertrophy, fibrosis, or atrophy.

Source: Adapted from Baldrick, 2026. Percentages calculated from n = 60 drug candidates.

The Findings Were Expected, but Still Actionable

The most commonly affected systems were consistent with the biology of small molecule oncology drugs, including cytotoxic effects on rapidly proliferating tissues and effects associated with pathway inhibition. Expected toxicity still requires interpretation. Sponsors must distinguish between findings that are pharmacology-related, stress-related, adaptive, monitorable, or potentially dose-limiting. That interpretation becomes the bridge between the toxicology study report and the clinical protocol.

Table 2. Converting toxicology observations into an IND-ready interpretation.

Pattern	Potential Meaning	Question to Address before IND Submission
Similar findings in both species	Potentially consistent pharmacology or shared target organ sensitivity	Does the exposure-response relationship support a manageable clinical starting dose?
Finding in one species only	Species-specific sensitivity, exposure difference, or unanticipated biology	Is the finding human-relevant, and how should uncertainty be addressed in monitoring?
Dose-related severity or incidence	Potential toxicologic threshold or dose-limiting liability	Can the dose rationale define a clinically acceptable margin?
Reversibility after recovery	Potential for recovery after stopping treatment	Does reversibility support dose escalation, interruption, or a monitoring strategy?
Incomplete or absent recovery	Potential longer-term tissue liability	Should the clinical protocol include organ-specific surveillance or exclusion criteria?

Species Selection and Comparative Toxicology

The dataset supports the continued value of comparative toxicology in oncology drug regulatory agency submissions. Although many target organs appeared in both rodent and non-rodent studies, species-specific findings were common. These differences can sharpen understanding of target organ sensitivity, exposure-toxicity relationships, and potential clinical relevance.

- Shared findings can strengthen confidence in expected toxicity patterns.
- Species-specific findings can reveal unexpected liabilities or differences in sensitivity.
- Discordant findings do not automatically weaken a testing package when the interpretation is clear.
- Regulators expect sponsors to explain why each species was appropriate and how findings translate to patients.

Consideration: When the toxicology package shows species differences, the goal is not to force equivalence; rather, the goal is to explain what the difference means for human risk, dose selection, and monitoring.

Dose Justification: Where Toxicology Becomes a Clinical Decision Tool

First-in-patient dose selection is one of the most important uses of the nonclinical package. In the reviewed programs, sponsors commonly reported safety level determinants from toxicology studies, such as severely toxic dose 10 (STD10) in rodents, highest non-severely toxic dose (HNSTD) in non-rodents, no observed adverse effect levels (NOAELs), where established, and in some cases, a maximum tolerated dose (MTD). For oncology programs, a NOAEL is not always essential, but a transparent dose rationale is essential.

Table 3. Safety level determinants reported in the 60-program evaluation.

Determinant	Rodent Findings	Non-Rodent Findings	IND Relevance
NOAEL	34/60 (57%)	37/60 (62%)	Often reported when established but not always required for oncology programs. Useful when it supports margin discussion.
STD10	35/60 (58%)	Not applicable	Common rodent determinant for small molecule oncology starting dose selection.
HNSTD	Not applicable	36/60 (60%)	Common non-rodent determinant when non-rodent data are most relevant to starting dose selection.
MTD	4/60 (7%)	3/60 (5%)	Used in a smaller number of studies, generally where tolerated dose boundaries were central to interpretation.

Source: Adapted from Baldrick, 2026. Some studies reported more than one determinant.

Translating Study Findings into Investigator Guidance

Toxicology findings become most valuable when they are translated into the Investigator's Brochure and clinical protocol in a way that is transparent and actionable. Target organ findings should inform clinical safety monitoring, dose escalation rules, and the sponsor's risk mitigation strategy.

Table 4. Examples of how nonclinical findings can inform clinical monitoring.

Nonclinical Signal	Potential Clinical Monitoring Focus	Interpretive Point
Lymphoid or hematologic findings	CBC with differential, infection surveillance, and immune status where appropriate	Does the exposure-response relationship support a manageable clinical starting dose?
Gastrointestinal findings	GI symptoms, hydration status, stool changes, supportive care plans	Is the finding human-relevant, and how should uncertainty be addressed in monitoring?
Liver findings	ALT, AST, bilirubin, alkaline phosphatase, clinical hepatic risk factors	Can the dose rationale define a clinically acceptable margin?
Kidney findings	Creatinine, BUN, urinalysis, electrolyte monitoring	Does reversibility support dose escalation, interruption, or a monitoring strategy?
Cardiovascular or ECG findings	ECG, QT/QTc, heart rate, cardiac history criteria	Should the clinical protocol include organ-specific surveillance or exclusion criteria?
Ocular or nervous system findings	Ophthalmic assessment or neurologic monitoring, where justified	are findings can be program-defining when irreversible or clinically severe.

Using 3Rs Thinking Without Weakening Regulatory Confidence

This evaluation of 60 small molecule oncology drug candidates raises an important strategic question: if many toxicities are expected and commonly repeated across programs, can the current nonclinical testing paradigm be optimized? The answer is not a blanket reduction in testing. The more useful framing is a set of open-ended 3Rs questions that help sponsors decide where replacement, reduction, or refinement may be scientifically defensible.

Table 5. Open-ended 3Rs questions for oncology IND-enabling toxicology strategy.

3Rs Lens	Question to Consider	How to Interpret the Answer
Replacement	Can *in vitro* assays, historical data, computational toxicology, or AI-informed approaches help identify expected target organ risks before animal studies?	Use as early screening and hypothesis generation. Replacement is strongest when the model is clearly relevant to the modality, target, and human biology.
Reduction	If dose-range-finding studies identify the same target organs as later GLP studies, can the study design be streamlined without compromising dose selection? Are two species routinely needed?	Consider only when the mode of action, exposure, clinical schedule, and regulatory expectations are well understood.
Reduction	Are recovery groups needed in every study, or only when reversibility meaningfully informs clinical risk management?	ICH S9 Q&A notes recovery groups should not automatically be included in all general toxicology studies.
Refinement	Can dose selection avoid excessively high-dose mortality that compromises interpretation and animal welfare? Can clinical scheduling, dosing holiday rationale, and monitoring endpoints be reflected more precisely in study design?	The dataset showed high-dose mortality in more than half of rodent and non-rodent studies, reinforcing the need for careful interpretation of dose range finding (DRFs) Alignment to the intended clinical plan strengthens both ethics and regulatory relevance.
Cross-cutting	What uncertainty remains after any optimization, and how will that uncertainty be managed clinically?	A streamlined package still needs a clear risk narrative, safety monitoring plan, and justification for any deviation from default expectations.

Strategic Takeaway: 3Rs optimization is strongest when framed as a scientific decision, not a cost-saving shortcut. The sponsor must demonstrate that any streamlined approach continues to protect patients and supports a credible first-in-patient plan.

Practical Checklist for a Regulatory Agency Acceptable Oncology Toxicology Package

- Is the study duration aligned to the proposed clinical schedule and ICH S9 expectations?
- Are the selected species justified by pharmacology, exposure, and human relevance?
- Are target organ findings clearly separated into expected pharmacology, adaptive findings, stress responses, and potential toxicities?
- Is dose selection supported by STD_{10}, HNSTD, NOAEL, MTD, exposure data, or a clear rationale for the selected approach?
- Are high-dose effects interpretable, or did mortality or poor condition compromise the value of the study?
- Are recovery groups included only where reversibility informs patient risk or clinical management?
- Does the Investigator's Brochure translate nonclinical signals into clear monitoring and risk mitigation language?
- Are 3Rs opportunities documented with a scientific rationale and a regulatory risk assessment?

How to Use These Insights

The considerations outlined in this white paper can support informed decision-making across multiple stages of early oncology development, including:

- **Early IND planning**, to anticipate target organ findings and align nonclinical strategy with regulatory expectations.
- **First-in-patient dose justification discussions**, by contextualizing toxicology data within a risk–benefit framework.
- **Investigator's Brochure development**, to clearly translate non-clinical findings into clinical guidance and monitoring strategies.

Conclusion: Nonclinical Toxicology as a Strategic Asset

Adverse toxicology study findings are not a barrier to the development of an oncology drug. When designed and interpreted within a risk-benefit framework, toxicology data enable informed decision-making, build regulatory confidence, and help sponsors enter first-in-patient studies with a clearer understanding of clinical risk. Across the 60-program evaluation, predictable target organ findings did not prevent clinical entry. They provided the evidence base for dose selection, investigator guidance, and patient monitoring.

Summary

Target-organ findings are expected in oncology toxicology programs for small-molecule drug candidates. The strategic question is not whether toxicity is present, but whether the nonclinical package clearly characterizes the risk to support first-in-patient dosing, investigator guidance, and a credible, narrative accepted by a regulatory agency.

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