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FDA Oncology Biologics Guidance: Nonclinical Safety Studies

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Executive Summary

The U.S. Food and Drug Administration (FDA) released a draft guidance on May 29, 2026 entitled **“Oncology Pharmaceuticals: Streamlined Nonclinical Safety Studies for Biologics and Conjugated Products”**. This guidance implements the FDA’s Animal Testing Reduction Roadmap and expands allowances for using fewer animals and alternative methods in nonclinical safety programs for certain oncology therapeutics. It specifically addresses performance of toxicology studies for (1) therapeutic biologics, (2) PD-(L)1 blocking monoclonal antibodies, (3) CD3-engaging bispecific antibodies, and (4) antibody-drug conjugates (ADCs) with cytotoxic payloads (www.lachmanconsultants.com) (www.globenewswire.com). The core recommendations encourage sponsors to utilize **single-species toxicology** approaches and **weight-of-evidence (WoE) assessments** — including in vitro assays, computational models, and other “new approach methodologies” (NAMs) — instead of traditional multi-species programs. Under the draft guidance, cases with only one relevant animal model (often the non-human primate) may suffice, and well-supported evaluations based on all available data can sometimes replace routine long-term primate studies (www.globenewswire.com) (xtalks.com).

This Sponsor **“playbook”** outlines these agency recommendations and offers a detailed analysis of their scientific rationale, practical implementation, and implications. We review corporate and regulatory perspectives, historical context, and emerging best practices. Data from past drug development and cutting-

edge science – including failure rates of animal-tested drugs, case examples like nivolumab and trastuzumab-emtansine, and international regulatory trends – are integrated throughout. Detailed sections cover: the FDA Roadmap and policy shifts; breakdown of the guidance's specific steering on each product class; definitions and examples of weight-of-evidence and NAMs; strategic planning for sponsors (pre-IND meetings, study design choices, justifications); case studies (e.g. PD-1 inhibitors, ADCs); statistical and evidence analyses; and broader implications for future drug development.

In sum, this comprehensive report serves both as an **in-depth research analysis** of the May 2026 draft guidance and as a practical strategic manual for sponsors aiming to align their programs with the new single-species and WoE paradigm.

Introduction and Background

Nonclinical safety evaluation is a critical phase in drug development, traditionally reliant on animal studies. For small-molecule drugs, international standards (e.g. ICH M3(R2)) often require toxicity studies in a rodent and a non-rodent species. For **biological therapies**, the ICH S6(R1) guideline (2009) likewise advocates a science-based approach, typically with studies in one pharmacologically relevant species (often non-human primates for human-specific targets) and a second species only if needed (docslib.org) (pdf4pro.com). In practice, however, many oncology biologics (monoclonal antibodies and related constructs) have historically been tested in two species or with extensive study designs, despite frequently lacking cross-species relevance. For example, checkpoint inhibitors (PD-1/PD-L1 antibodies) or T-cell engagers may only bind primate targets, rendering rodent studies superfluous.

Meanwhile, preclinical pipeline terminations are common: **"over 90% of drugs safe in animal studies fail in humans"** (www.fda.gov), underscoring the limitations of traditional animal models. Non-human primate (NHP) studies, while often considered the "gold standard" for human-like immunology, are especially constrained by differences from human disease and ethical and logistical costs. Recognizing these issues, regulators and scientists have called for a shift toward human-relevant methods. In April 2025, for instance, the FDA issued a news release announcing a **roadmap to phase out routine animal testing for monoclonal antibodies and other drugs**, explicitly promoting computational models and human cells/organoids (NAMs) to predict safety (www.fda.gov). By April 2026 the FDA reported achieving its first-year roadmap goals, including draft guidance on reducing or eliminating nonhuman primate testing in monoclonal antibody development, draft guidance on weight-of-evidence approaches to support NAMs, and a searchable database of where alternative methods are acceptable (www.fda.gov). Similarly, globally, the EMA and other agencies have advanced 3Rs initiatives. The EMA's Innovation Task Force now encourages "replace, reduce, refine" methodologies (organoids, organ-on-chip, in silico) and offers early scientific advice on NAMs (www.ema.europa.eu). The UK's MHRA recently published guidance committing to 3Rs and allowing case-by-case exceptions to traditional animal tests if scientifically justified (www.gov.uk).

Against this backdrop, the FDA's May 2026 draft guidance represents a tangible extension of international trends into a specific "oncology biologics" context. It follows **ICH S9** for anticancer drugs (which streamlined requirements for small-molecule oncology agents) and supplements FDA's own previous guidances (e.g. on therapeutic radiopharmaceuticals). The new guidance is intentionally *narrow* (focusing on oncology biologics and conjugates) and *non-binding*, but it signals the agency's expectation that sponsors should exploit all

appropriate evidence and high-tech methods to minimize animal use. According to the FDA's guidance page, the streamlined approaches "provide safety information that is equivalent or superior to animal studies" and "will result in more efficient product development" (www.fda.gov).The remaining sections detail these approaches in depth, focusing on each product class, the concept of single-species programs, and weight-of-evidence frameworks, illustrated with data and examples.

The FDA Animal Testing Reduction Roadmap

As a framing element, the guidance is a direct outgrowth of the FDA's April 2025 **Roadmap to Reducing Animal Testing in Preclinical Safety Studies**. That roadmap set ambitious goals — for example, to phase out default animal requirements when robust alternatives exist — and to set time-bound targets to act on them. A key early action was the April 2025 announcement that the FDA would "eliminate unnecessary animal testing" for monoclonal antibody therapies and other drugs (www.fda.gov). This announcement pledged to leverage **artificial intelligence models, human organoid lab systems, and real-world human data** to assess safety instead of repeating animal tests (www.fda.gov). Notably, it stated that IND applications could *immediately* begin incorporating NAMs and non-animal data, with sponsor-provided human-based evidence potentially earning "streamlined review" by the FDA (www.fda.gov). A year later (April 2026), the FDA reported on its Year One progress of the roadmap: among other measures, it highlighted release of draft guidances on NHP reduction in antibody development, expansion of weight-of-evidence (WoE) approaches, and launch of a searchable database clarifying where alternative methods are acceptable (www.fda.gov). The FDA's release states that more than **90% of drugs that clear animal studies do not receive FDA approval** (www.fda.gov), and therefore better human-relevant methods can accelerate safer treatments. These themes — reliance on WoE and NAMs, reduction of NHP use, and industry incentives to adopt alternatives — are echoed in the new oncology guidance.

In sum, sponsors are now operating in a regulatory environment that strongly encourages innovation and flexibility. FDA statements emphasize that data from prior human experience or well-understood targets can allow skipping certain animal tests, and that early dialogues with the agency are expected when proposing non-traditional safety programs. An FDA press release explicitly quoted Dr. Angelo de Claro (OCE Director) stating that the draft guidance "fulfills the agency's promise to reduce the use of animal testing" and advances "a more efficient drug development process" by endorsing single-species and evidence-based approaches (www.fda.gov). Similarly, independent analysts have noted that sponsors should be prepared to "explain the science" behind streamlined programs and discuss them with FDA "early" in development (xtalks.com). The rest of this report follows these cues to give sponsors a playbook on how to implement the guidance's recommendations.

Scope of the Guidance

The draft guidance is specifically scoped to *oncology therapeutics that are biologics or conjugated products*. This includes four distinct categories:

- **Monospecific Biologics (General)** – Therapeutic biologics (primarily monoclonal antibodies or recombinant proteins) targeting a single molecular target, used in cancer treatment, *excluding* the special categories below.
- **PD-(L)1 Blocking Antibodies** – Monoclonal antibodies that target the PD-1/PD-L1 immune checkpoint pathway (e.g., anti–PD-1 or anti–PD-L1 mAbs) in oncology.
- **CD3 Bispecific T-Cell Engagers** – Bispecific antibodies that engage CD3 on T cells to bring them into contact with tumor cells (e.g., BiTE® molecules).
- **Antibody–Drug Conjugates (ADCs)** – Antibodies conjugated to cytotoxic small-molecule payloads, delivering chemotherapy specifically to tumor cells.

These categories are explicitly listed in the guidance and reflect both scientific considerations and historical patterns. As summarized by industry commentary, the FDA "provides recommendations for the following oncology and conjugated products: *Biologics*, *PD-(L)1 blocking monospecific antibodies*, *CD3 bispecific T-cell engagers*, and *ADCs with cytotoxic payloads* (www.lachmanconsultants.com)." For each of these, the guidance specifies how a sponsor may deviate from traditional two-species toxicology paradigms by using a single relevant species or by performing a WoE assessment in lieu of some animal studies. The guidance's core is about general toxicology study reductions and weight-of-evidence risk assessments.

Importantly, this guidance is in *draft* form and non-binding (www.fda.gov). The comment period on the draft closed in late July 2026 (the Federal Register notice gives July 31, 2026 (www.govinfo.gov)). Thus it represents FDA's current thinking and recommendation, but sponsors must still justify any alternative approach in their IND/IMPD or BLA submissions. The guidance makes clear that *"CDER oncology review divisions will determine whether the information included in the WoE risk assessment is sufficient to address safety risks based on the totality of evidence"* (www.lachmanconsultants.com). In practice, this means each case will be evaluated individually. However, the guidance provides a structured roadmap — a true "playbook" — of what kinds of data and reasoning the FDA expects from sponsors in proposing streamlined safety programs.

Traditional Nonclinical Study Practices

Before delving into the streamlined approaches, it is useful to contrast with traditional nonclinical study designs for these product classes:

- **Monospecific Biologics:** Conventional practice often aligns with ICH S6(R1): one relevant species (typically cynomolgus monkeys or another primate) is the primary toxicology model, supplemented by a rodent (usually rat) if the biologic cross-reacts in rodents or if additional data on off-target effects is needed. General toxicology typically includes repeated-dose studies (e.g. 4-week and 13-week for chronic, plus possibly 26-week studies) in both sexes of each species. Secondary pharmacology (effects on immune response, cardiovascular, neuro) and safety pharmacology (vital organ function) studies may also be done. Genotoxicity and carcinogenicity studies are usually waived for these cancer indications, per ICH S6 allowance (docslib.org). If the biologic is an antibody, in vitro immune cell assays (e.g. cytokine release) may be standard.

- **PD-(L)1 Antibodies:** Anti–PD-1/PD-L1 mAbs typically *only* bind human and primate PD-1/PD-L1. Rats and mice lack cross-reactivity, so rodents are usually not pharmacologically relevant. In practice, toxicology programs for drugs like nivolumab or pembrolizumab have centered on cynomolgus monkeys (with perhaps surrogate-mouse efficacy models separate). For example, the FDA review of nivolumab notes it was tested in 4-week and 13-week cynomolgus studies, with no rodent toxicology because the mouse version was a separate surrogate (docslib.org). Such programs might also include a pregnancy study in monkeys if relevant.
- **CD3 Bispecifics:** Agents that bind CD3 on T cells generally cross-react with rodents (rodents have CD3), so rats or mice can be used. However, higher-order primates share more similar immune systems. Traditional testing often includes one rodent and one non-rodent (monkey) species for repeat-dose toxicity. Because CD3-bispecifics activate immune cells, even short-term exposure can have profound effects (cytokine release, lymphoid organ changes). Thus, historical safety programs often included intensive monitoring (e.g. telemetry, extended immunophenotyping) in at least monkeys. A 13-week monkey study was typical, although sometimes sponsors did only a 4-week monkey study if risk could be assessed.
- **ADCs (Cytotoxic Payload):** ADCs combine a targeting Ab with a cytotoxic small-molecule. If the antibody portion is active only in primates, monkeys are the main “target” species. However, small payloads (e.g. DM1, SN-38) have systemic toxicities independent of the Ab. Traditional practice has been to run toxicology in **two species**: rodents (rats or mice) to characterize payload-related and off-target effects, and non-rodents (usually monkeys) for target-related effects. For instance, trastuzumab emtansine (T-DM1) was studied in rats *and* monkeys (www.sciencedirect.com) because T-DM1 binds primate HER2 but not rodent neu. In general, for ADCs the industry often sees two-species full studies as needed unless a strong justification is given.

These approaches have yielded useful data but at high cost — in time, animals, and often limited predictivity. The new draft guidance now allows sponsors to question whether such full programs are always needed.

Summary of Draft Guidance Recommendations

The May 2026 draft guidance contains the following **key themes and recommendations**:

- **Single Relevant Species**: When possible, conduct general toxicology in *one species only*, rather than two. In practice, this usually means relying on the single pharmacologically relevant species (e.g. cynomolgus monkey for human-specific targets). The guidance explicitly endorses replacing “two-species” programs with one-species programs when justified by target biology and prior knowledge (www.fda.gov) (www.globenewswire.com). For example, if an antibody binds only human/primate and not rodents, the sponsor should focus on monkey studies and can often omit rodents.
- **Weight-of-Evidence (WoE) Assessments**: Sponsors may replace conventional animal studies with a holistic evaluation of all available data. A WoE assessment integrates in vitro assays, mechanistic pharmacology, published literature, results from similar drugs, clinical data (if available), and computational models. The guidance advises that a 3-month monkey study might be replaced by a

WoE-based safety assessment when appropriate (www.globenewswire.com) (xtalks.com). Notably, *New Approach Methodologies* (NAMs) — such as organ-on-chip, human cell assays, and in silico models — are explicitly included as part of WoE. The FDA has noted that NAM integration has advanced under its 2025 roadmap, and named WoE plus NAMs as a pathway to reduce NHP use (www.globenewswire.com) (www.fda.gov).

- **Eliminating Unnecessary Studies**: Animal testing may be skipped entirely if there is no pharmacologic rationale. For example, if a drug has no binding or activity in a given species, testing in that species is "unnecessary" (www.globenewswire.com). In plain terms, if an oncology biologic does not cross-react with a rodent, sponsors should not perform ineffective rodent studies. Similarly, if a class of drugs is already well understood (e.g. several approved PD-1 inhibitors), the guidance encourages assessing whether repeating animal studies adds new safety information. The FDA suggests that in such cases evidence-based reviews *can substitute* for new studies (www.globenewswire.com) (xtalks.com). Overall, the overarching message is that *sponsors should not default to animal studies by reflex*: they should justify each study or omission in terms of scientific need.
- **Incorporation of NAMs**: The guidance explicitly encourages use of NAMs within WoE. NAMs include any advanced non-animal method that can provide human-relevant safety data (e.g. microphysiological systems, human-cell assays, AI toxicology models). The draft states that WoE risk assessments *"may include New Approach Methodologies, as appropriate"* (www.globenewswire.com). This echoes FDA statements in the roadmap year-one report promoting advanced in vitro, AI, and other human-centric methods (www.fda.gov). While the guidance does not enumerate which NAMs are acceptable — that is expected to be case-dependent — it signals that innovation in testing can strengthen the evidentiary package.
- **Product Class-Specific Points**: While the above apply broadly, the guidance also spells out particular points for each class of products (see next sections). For example, it notes that PD-(L)1 and CD3 agents, as a category, may warrant reductions in long-term monkey studies. For ADCs, it suggests that if a cytotoxin is well-studied, sponsors might rely on simpler rodent data (xtalks.com). For general biologics, it reiterates that two-species is not always needed if a WoE is strong.

In addition to these content recommendations, the guidance clarifies procedural matters: it is for industry guidance only (non-binding), and FDA review divisions will make the final determination on sufficiency of any proposed program (www.lachmanconsultants.com). Sponsors are strongly advised to **engage early** with FDA (e.g. at Pre-IND or End-of-Phase meetings) to discuss these nontraditional plans. In fact, one industry analysis explicitly notes that sponsors *should explain their scientific rationale and seek FDA feedback early* when employing a WoE approach (xtalks.com).

The following sections unpack the guidance's thrust in detail for each product category and for WoE practices, supported by examples and data.

Table 1: Nonclinical Safety Study Recommendations by Product Type

Product Category	Traditional Nonclinical Program	Draft Guidance (Single-Species / WoE)
Monospecific Oncology Biologics (Non-checkpoint targets)	Typically 2 species: rodent (e.g. rat) + non-rodent (usually NHP) for general toxicity. Repeated-dose tox (e.g. 4-4-13 wk studies). Reproductive tox in appropriate species. Genotox waived (ICH S6).	For biologics with pharmacological activity similar to humans in both rodent and non-rodent species, 1- and 3-month general toxicology studies may be conducted in a single rodent species, supplemented with a WoE risk assessment as appropriate (www.fda.gov) (www.globenewswire.com).
PD-(L)1 Immune Checkpoint Inhibitors	Monkeys only (rodents are non-reactive). Repeated tox in cynomolgus (4-wk, 13-wk). Often dedicated reproductive tox in monkeys. Mechanistic assays (e.g. cytokine release in human PBMCs).	The draft guidance states that the chronic-effects assessment may be based on a WoE risk assessment in lieu of a 3-month toxicology study; with justification, the 1-month study may be non-sacrificial and supplemented with a WoE risk assessment (www.globenewswire.com) (xtalks.com). For example, PD-1/KO mouse infection data in label provide context (dailymed.nlm.nih.gov). WoE can cover immune-related risks so long-term NHP studies can be shortened or replaced.
CD3 Bispecific T-Cell Engagers	Typically two species (rodent + NHP) unless rodent irrelevant. Immune activation is main risk. Standard: e.g. single biomodal repeat-dose (4-wk and 13-wk in monkeys; short rodent study if antigen reactivity). Frequent monitoring of cytokines, T cell counts.	For CD3 bispecifics, the draft guidance states that the chronic-effects assessment may be based on a WoE risk assessment in lieu of a 3-month toxicology study (xtalks.com). The following is the author's commentary, not guidance text: sponsors may wish to build WoE packages (e.g. in vitro T-cell activation assays, data from similar agents) to support such a justification. The draft describes a non-sacrificial option only for the 1-month study of PD-(L)1 blocking antibodies, not for CD3 bispecifics.
ADCs (Cytotoxic payloads)	Two-species: usually rat + monkey. Rodent studies characterize payload toxicity, NHP for antibody-target effects. E.g., T-DM1 did full 2-species studies (www.sciencedirect.com). Traditional ICH general and chronic tox plus payload evaluations.	Often **rodent-only** if justified. If the payload's pharmacology is well-known (from similar drugs) and the antibody target biology is straightforward, sponsors may propose using only a rodent (since primate ⇒ same payload toxicity). For example, FDA suggests that in ADCs the cytotoxin's known profile can allow skipping NHP or replacing with WoE (xtalks.com). One could argue that a single species (rodent) covers both target-independent and –dependent toxicity when weight-of-evidence (pharmacokinetics/mechanism) is robust (www.sciencedirect.com). A WoE plan might include exposing data on payload mechanisms to justify modifications.

Note: "WoE" = Weight of Evidence; includes all relevant nonclinical, clinical, literature, and NAM data. The guidance advises sponsors to present comprehensive risk assessments when proposing reduced testing. FDA regulators will judge each case based on this totality of evidence (www.lachmanconsultants.com) (xtalks.com).

Single-Species Toxicology Approaches

Under the new draft guidance, sponsors are encouraged to base toxicology programs on **a single pharmacologically relevant species** whenever scientifically justified. This contrasts with older paradigms that commonly used two species by default. The guidance rationale is that at least in oncology biologics, one high-

quality species can often capture the critical safety signals if chosen correctly. As FDA's press release states, where a "single relevant species" can provide necessary data, sponsors should consider that instead of two (www.globenewswire.com).

Application: In practice, this single-species approach means:

- If the biologic binds human and only one animal species (e.g. cynomolgus monkey), **that one species suffices** for general toxicology. No need for a "safety filler" second species if it is not pharmacologically responsive. For example, both nivolumab and pembrolizumab programs used only cynos for repeat-dose toxicity because rodent species were unresponsive (docslib.org).
- If a biologic cross-reacts with rodents *and* NHPs (less common for human-specific targets), the sponsor could still justify using only one if the totality of evidence supports it. The guidance suggests a WoE justification could cover why a second species adds little new information (www.globenewswire.com).
- For PD-1/PD-L1 blockers, only one species (monkey) is relevant, and even within that, sponsors may further argue that some routine studies are not needed. The draft suggests even skipping the standard 3-month monkey study if a strong WoE risk assessment exists (www.globenewswire.com).
- For CD3 bispecifics, the draft guidance says that an assessment of chronic effects may be based on a WoE risk assessment in lieu of a 3-month toxicology study. The guidance text does not address rodent studies for CD3 agents or a single-species program for them; any such approach would be a sponsor proposal to justify with FDA, not a guidance recommendation.

A practical sponsor play: At Pre-IND, present the target-binding data: e.g. "We have demonstrated that our antibody binds human and cyno target but not rodent: thus cyno is the only relevant species." Then outline a minimal toxicology program (e.g. 4-week and 13-week studies in cynos) with justification. Emphasize existing knowledge (literature on target, similar drugs). If proposing to omit a rodent, cite guidance language: "animal testing may be unnecessary because there is no binding" (www.globenewswire.com). If suggesting a shorter (e.g. 4-week only) monkey study instead of a 13-week, build that as a WoE argument.

Illustrative Example – Nivolumab (Opdivo): This fully human anti–PD-1 IgG4 antibody binds human PD-1 and cynomolgus PD-1 but not rodent PD-1 (docslib.org). In its development program, Bristol-Myers Squibb tested nivolumab only in cynos for general toxicity (4-week and 13-week studies in monkeys) and did not conduct separate rodent chronic tox studies (docslib.org). The FDA's 2014 pharmacology/toxicology review of nivolumab notes that "general toxicology studies… were conducted in cynomolgus monkeys," that exposure at all dose levels exceeded human exposure at the intended clinical dose, and that toxicities were limited to mild increases in monocytic and lymphocytic infiltration of tissues (FDA Drugs@FDA review). Consistent with ICH S6(R1), no genotoxicity or carcinogenicity studies were done (docslib.org). Under the new draft guidance, a sponsor could emulate this approach: perform the essential monkey studies and cite existing knowledge (published human clinical safety data, related PD-1 mAbs) as *weight-of-evidence* to argue against additional species testing.

Table 2: Case Studies of Nonclinical Plans

Drug/Product	Class/Mechanism	Traditional Nonclinical Program	Hypothetical Streamlined Plan (Illustrative Only)	Key References
Nivolumab (Opdivo)	Anti–PD-1 monoclonal antibody	4-week & 13-week toxicity studies in cynomolgus monkeys (no rodent) (docslib.org); safety pharmacology in cynos. No genotox/carcinogenicity (ICH S6) (docslib.org).	One-species (cynomolgus) only: e.g. 13-week cyno study (as done); omit any rodent tox. Use PD-1/KO mouse data and clinical safety reports as weight-of-evidence. Sponsor would cite guidance to support no rodent needed ("no binding" in rodent) (docslib.org) (www.globenewswire.com).	Nivolumab pharmacology review (linked in this row).
Avelumab (Bavencio)	Anti–PD-L1 monoclonal antibody	The label describes a 3-month repeat-dose toxicity study in cynomolgus monkeys, which included assessment of male and female reproductive organs (dailymed.nlm.nih.gov).	Under the draft guidance, a WoE risk assessment may replace the 3-month toxicology study for PD-(L)1 blocking antibodies.	Bavencio (avelumab) label, DailyMed (linked in this row).
Trastuzumab emtansine (T-DM1)	HER2-targeted ADC with DM1 payload	Two species: Repeated-dose tox in both rats (antigen-negative; DM1 effects) and cyno monkeys (HER2-positive; ADC + DM1 effects) (www.sciencedirect.com). Additional single-dose studies of unconjugated DM1 in rats. Toxicities included hepatic and hematologic effects (www.sciencedirect.com).	Purely hypothetical illustration (not an FDA-endorsed plan, and not a conclusion that the ADC would meet the guidance's conditions): since DM1 is well-characterized (toxic to marrow, liver) from other studies, sponsor could propose single-species (rat) program. For HER2-dependent effects, use in vitro human data. A WoE risk assessment (including human organoid hepatotoxicity studies or known T-DM1 clinical data (www.sciencedirect.com)) could allow omitting monkey or reducing its duration.	T-DM1 preclinical safety paper (linked in this row).

Note: These examples illustrate how sponsors can leverage the guidance. In each case, the **streamlined plan** replaces a second species or long-term study with a weight-of-evidence justification, as a hypothetical illustration of the kind of weight-of-evidence argument a sponsor might make under the non-binding draft guidance. These are the author's illustrations, not FDA-endorsed or FDA-accepted plans for these products; the cited sources document each product's historical nonclinical program, not any FDA assessment of the streamlined plans.

Weight-of-Evidence and New Approach Methodologies

A central innovation of the draft guidance is **formalizing the "Weight-of-Evidence" (WoE) approach** as a viable alternative to standard animal testing. As described in the guidance and accompanying communications, a WoE assessment means assembling *all relevant data sources* to assess safety, rather than insisting on predefined animal studies. This concept is detailed in breakout texts from FDA sources:

- The FDA explains WoE as "looking at the full body of available evidence instead of relying only on new animal studies" (xtalks.com).
- This evidence includes: **laboratory and safety data on the investigational drug**, known information about the drug's molecular target, peer-reviewed literature on toxicity, and **safety findings from similar approved drugs** (xtalks.com).
- Critically, NAMs such as human cell or tissue assays, organ-on-chip experiments, and computational toxicology models *count as evidence*. The Xtalks article summarizes: *"These assessments may also include New Approach Methodologies…that can provide additional safety information."* (xtalks.com).
- For well-characterized target classes, a WoE approach "may sometimes replace a three-month animal toxicology study" (xtalks.com).

A Narrated Example: If developing a new anti-CD3 bispecific, a sponsor might collect WoE components such as: extensive in vitro T-cell activation assays (including human PBMC cytokine release); published toxicity profiles of other CD3 bispecifics (e.g. neurological or CRS events); pharmacokinetic modeling; and any in vivo short-term data available. This integrated dossier could then underpin safety conclusions, potentially replacing one or more routine animal studies. The draft guidance explicitly acknowledges that *"these evidence-based approaches"* may be sufficient to address safety (www.fda.gov) (xtalks.com).

New Approach Methodologies (NAMs) are specially highlighted as part of WoE. The FDA defines NAMs broadly as innovative methods that can replace or augment animal tests (e.g. advanced in vitro, in silico, organ systems) (www.fda.gov). The guidance notes that NAMs "may be included" in WoE assessments (www.globenewswire.com). FDA's press releases and reports frequently mention NAMs: for example, the Year One roadmap report highlighted "incorporate in vitro assays, computational toxicology, and other human-relevant models" as part of WoE (www.fda.gov). EMA's similar initiatives also reference organoids and chips (www.ema.europa.eu). Thus, sponsors are encouraged to incorporate any qualified NAMs relevant to their product, such as:

- Human cell-based assays (e.g. liver spheroids for hepatotoxicity, T-cell activation on microfluidic devices).
- Organ-on-a-chip models (e.g. microphysiological cardiac or vascular models if cardiotoxicity is a concern).
- In vitro systems for developmental or immune effects.
- In silico models (QSAR, PBPK, or AI-toxicology platforms) that can predict toxicity endpoints.
- High-throughput screening data (if available) from similar structures.

However, sponsors must be cautious: NAMs are not universally validated for all endpoints, so they should be used in support of, not as an unsupervised replacement for, regulatory endpoints. The draft guidance itself does not provide a checklist of acceptable NAMs, so sponsors should justify their choices and cite validation status where possible. Engaging early with the FDA Innovation Office or other tool-qualification pathways (e.g. FDA's DDT/NAMS programs) can clarify what NAM data will be acceptable.

From a practical standpoint, preparing a WoE dossier involves systematic literature review and data integration. Sponsors should document existing knowledge of the target (e.g. biology of PD-1 blockade, etc.) and analogs. They should gather any decentralized data: published history of class effects, any clinical or preclinical safety signals in related products, and mechanistic insights. Modern publishing databases, proprietary safety databases, and even publicly reported IND disclosures can feed into this. For example, known adverse events for PD-1 inhibitors (pneumonitis, colitis, endocrine disorders) are well documented in the clinic, and any animal findings of immune toxicity provide context. A sponsor might also perform targeted in vitro assays (e.g. T-cell redirection potency, cytokine profiling, off-target binding panels) to strengthen the WoE. All such data then allow a rationale such as, *"We anticipate no new class-specific toxicities beyond those already characterized, and prior experience shows utilities in humans that align with our findings."* Combined with quantitative PK/PD modeling, this can often obviate the need for additional long-term animal studies.

It is critical in a WoE approach to articulate not just positives (what data support product safety) but also to address residual uncertainties. If, for example, a hypothesis-driven concern remains (e.g. novel immune toxicity), the sponsor can propose a targeted short study to test that specific risk, rather than broad screening. This use of focused rather than glancing studies exemplifies a WoE philosophy. The draft guidance encourages transparency: sponsors should **"explain the science behind these choices"** (xtalks.com). Concretely, a WoE plan might be submitted as part of the IND/CTA package with a narrative or risk assessment report, summarizing all data and concluding why certain studies are unneeded or why a regimen is sufficiently safe.

Detailed Recommendations by Product Class

Below we expand on guidance specifics for each product category, with citations:

Monospecific Oncology Biologics (General Targets)

For conventional monoclonal antibodies or proteins (excluding the checkpoint and bispecific categories), the guidance reiterates the **one-relevant-species principle**. Key points:

- If a nonclinical program historically would have used two species, sponsors may now justify a single species if there is scientific rationale. The typical relevant species is usually the cynomolgus monkey (or sometimes chimpanzee/baboon, though rare) if it closely mimics human target binding. Otherwise, an immunocompetent rodent or transgenic rodent might serve as the relevant species.

- If the antibody binds only humans/primate, rodent studies can be foregone. The guidance's example about "no binding or pharmacologic activity" directly applies (www.globenewswire.com): a sponsor should simply state that the agent has no cross-react in rodents, making such studies uninformative.
- Even when two species are possible, sponsors should evaluate whether the second species provides any new insight. For biologics that are pharmacologically active in both a rodent and a non-rodent species, the draft guidance says general toxicology (1- and 3-month) studies may be conducted in a single rodent species, supplemented with a WoE risk assessment as appropriate.
- Reproductive/developmental toxicity: The draft guidance does not address these endpoints; what follows is the author's commentary based on ICH S6(R1), not guidance content. If rodents are the only cross-reactive species for reproductive endpoints, a sponsor might justify not performing a primate fertility study if the target is a self-antigen and human pharma data exist (an exception to be discussed). Note: ICH S6(R1) already allows flexibility for reproductive tox if not needed for safety.
- **Example:** A therapeutic anti-EGFR antibody (similar to cetuximab) might only bind primate EGFR and not rodent EGF receptor cross-reactively, in which case the monkey would be the only pharmacologically relevant species. If such an antibody were instead active in both a rodent and a non-rodent species, the draft guidance says the 1- and 3-month general toxicology studies may be conducted in a single rodent species. If historical data from cetuximab shows no unexpected hits in monkeys, one could make a WoE case to reduce or eliminate certain long-term monkey studies.

PD-(L)1 Immune Checkpoint Inhibitors

This category includes all PD-1 or PD-L1 blocking monoclonal antibodies used in oncology. Their nonclinical evaluation has particular features:

- **Species Choice:** Rodents do not respond to human PD-1/PD-L1, so cynomolgus monkeys are the only relevant species for pharmacology/tox. Thus, traditionally only monkeys were used. The draft guidance confirms this and explicitly mentions PD-(L)1 inhibitors as a class for streamlined approaches (www.lachmanconsultants.com).
- **Study Design:** Historically, sponsors often did 4-week and 13-week monkey studies. The new guidance suggests that, with adequate WoE, even a shorter study could suffice. In particular, the guidance notes replacing a "three-month NHP study" with a WoE risk assessment is an option (www.globenewswire.com).
- **Evidence Integration:** Because many PD-(L)1 therapies are on the market, a sponsor can leverage published clinical safety data (e.g. incidence of pneumonitis, colitis) as part of WoE. As Xtalks notes, *"For some PD-(L)1 blocking antibodies… [evidence-based approach] may replace some three-month animal toxicology studies"* (xtalks.com).
- **Animal Efficacy Models:** Human transgenic mouse models (e.g. mice with human PD-L1) are sometimes used experimentally, but regulatory bodies typically do not require surrogate rodent models for toxicology. That practice is not changed by the draft.
- **Case in Point – Nivolumab:** As discussed above, nivolumab's program (active in monkeys, not in rodents) exemplifies the approach. Under the guidance, any decision to rely on a single species is a sponsor judgment to be justified and discussed with FDA.

- **Pregnancy/Repro:** The draft guidance does not address pregnancy outcomes or reproductive toxicity, so existing practices are unchanged; the remainder of this bullet is the author's commentary based on ICH S6(R1). Reproductive toxicity should still be assessed if the product could reach pregnant patients; sponsors should discuss any proposal to modify reproductive toxicity testing with FDA rather than assume it can be omitted.

CD3 Bispecific T-Cell Engagers

Bispecific antibodies engaging CD3 on T cells (to redirect immune cells to tumors) are high-potency immunostimulants. The guidance's treatment of this class is similar to PD-(L)1: they may qualify for single-species WoE strategies.

- **Species Reactivity:** CD3 bispecifics differ in which species they cross-react with, so the relevant animal species must be established product by product. Blinatumomab is an example of a highly species-selective molecule: in the PMDA review summary, B and T cells from cynomolgus monkeys, rhesus monkeys, baboons, dogs and mice did not detectably bind it, so animal work with it relied on a murine surrogate molecule rather than on cross-reactivity. Where a CD3 bispecific does cross-react with a non-human primate species, primate immune systems more closely mirror human immune responses, so that species is typically the pharmacologically relevant one. Under the draft guidance, a sponsor could argue to use *only monkeys* if justified. The guidance explicitly lists "CD3 bispecific T-cell engagers" as covered (www.lachmanconsultants.com), indicating regulators expect these to be evaluated with similar flexibility.
- **Cytokine Release Syndrome (CRS) Consideration:** A major concern with CD3 therapies is cytokine storm. In prior programs, sponsors sometimes conducted acute/45-minute or few-hour mouse and monkey studies, plus longer repeat-dose. Under the new approach, sponsors should still do acute cytokine-release studies (in vitro or in vivo) but, as an illustrative design not taken from the guidance, may do a single short repeat-dose in NHP (e.g. 2-4 weeks). The draft itself says only that chronic effects may be assessed by a WoE risk assessment in lieu of a 3-month toxicology study. The emphasis is on safety at the first doses, not necessarily chronic "cancer" toxicities.
- **Weight-of-Evidence with CRS Data:** The guidance envisions that if a sponsor has thorough in vitro characterization of T-cell activation and CRS risk (e.g. human PBMC cytokine panels, microfluidic immune system chips), these can form part of the Safety assessment. The Xtalks piece explicitly states that for CD3 bispecifics, the WoE may replace some traditional toxicology studies (xtalks.com). Practically, a sponsor might plan only a 4-week cyno study with extensive monitoring, and use WoE (including published safety of blinatumomab and other BiTEs) to argue that no further 13-week study is needed.
- **Example – Blinatumomab (BiTE):** Blinatumomab is a CD3/CD19 bispecific T-cell engager and is used here only as an illustrative example of the class; any reduced nonclinical program for a similar product would be the sponsor's own proposal, to be discussed with FDA. The sponsor could cite WoE including its own IND human data and literature that no new unexpected toxicity emerged in late trials.
- **Other Considerations:** Sponsors should note that immunogenicity remains a concern for any BiTE, so anti-drug antibody (ADA) analyses are important. If WoE suggests, some immunotoxicology endpoints (autoimmunity, etc.) might be omitted from animal study designs if the mechanism is well understood

and any similar products have well-characterized outcomes.

Antibody–Drug Conjugates (ADCs) with Cytotoxic Payloads

ADCs are hybrids of biologics and small molecules, so they pose unique challenges. The guidance specifically mentions **ADCs with cytotoxic payloads**, recognizing the dual nature of these agents. Recommendations include:

- **Species Selection:** Since ADCs have both target-mediated (antibody) and target-independent (payload) effects, historically two species were used: typically rat (payload-relevant but target-agnostic) and monkey (target+payload). Under the new guidance, sponsors may justify using **only one species** if a weight-of-evidence justification covers the other. The draft guidance limits this option: when the payload's safety is well characterized (e.g., the same payload as in approved ADCs) and the payload is the main driver of toxicities, the 3-month toxicology study may be conducted in rodents only, and when the antibody's target is novel and not bound in the rodent species, a WoE risk assessment should also be submitted.
- **Payload Expertise:** The guidance hints that known payload properties can allow simplification. The Xtalks summary says for ADCs "rodent studies may be enough in some cases if the payload is already well characterized from other approved drugs" (xtalks.com). This means: if the small-molecule cytotoxin (e.g. DM1 in T-DM1 or MMAE in brentuximab vedotin) has an established human safety profile from other agents, the sponsor can cite that data to support reducing animal tests. A strong case could be: "This payload causes bone marrow and GI toxicity (known from prior compounds); our conjugate behaves similarly in vitro; therefore, an additional 13-week monkey study is not likely to identify new hazards beyond those covered by a rodent program."
- **Example – Trastuzumab Emtansine:** A published preclinical safety paper (Flagella et al., 2013) reports that T-DM1 was studied in rats and monkeys for different endpoints. T-DM1 binds primate HER2 but not rodent. As the author's illustration rather than guidance content, a T-DM1-like conjugate could use the rodent-only option only if it met the draft's conditions (a well-characterized payload that is the main driver of toxicities), with a WoE risk assessment where the novel target is not bound in rodent. This aligns with the guidance's suggestion that ADC toxicity has been well studied and can sometimes use reduced animal models (xtalks.com) (www.sciencedirect.com).
- **ADC-Specific WoE:** Additional WoE components for ADCs include the **toxicokinetics** (how much free payload appears in circulation, etc.), the stability of the linker (how much payload actually reaches non-tumor tissues), and known off-target expression of the antibody's antigen. Sponsors should include in vitro data on ADC internalization kinetics, in vivo PK/PD bridging studies, and literature on tissue cross-reactivity. If data indicate minimal premature payload release, one could argue that systemic payload exposure (and thus rodent model) already covers off-target risks.
- **Satellite Studies (author's illustration, not guidance content):** Even if a sponsor forgoes a full monkey study, a shorter mechanistic study may still be worth considering. A compromise might be a single-dose or 4-week monkey study to survey major organ effects, then use WoE for longer exposure scenarios. The guiding principle is to tailor studies to address key uncertainties, rather than to confirm everything.

In summary, for ADCs the sponsor playbook is to emphasize understanding of the cytotoxic component and reuse existing safety knowledge about it, using that as evidence to reduce new animal tests. Weight-of-evidence should explain how the conjugate's safety profile is predictable from its parts and from analogous therapies.

Sponsor Strategies and Implementation

To translate the guidance into practice, sponsors should approach development strategically. Key steps in the **Sponsor Playbook** include:

1. **Early Regulatory Engagement:** As repeated by FDA and experts, sponsors are advised to **discuss proposed safety plans early** (Pre-IND or Type B meetings). Outline the single-species or WoE strategy with scientific rationale, and seek FDA input. The agency's draft explicitly encourages early discussions of these alternative approaches (xtalks.com).
2. **Characterize Target and Cross-Reactivity:** Generate robust in vitro data on the drug's binding/bioactivity across species. Identify the *single relevant species* (e.g. which species expresses the target and is pharmacologically responsive). Any lack of cross-reactivity should be clearly documented (e.g. receptor binding assays showing no rodent binding). This justifies skipping those species.
3. **Aggregate Existing Data:** Compile all known safety data: Published toxicities/side effects of drugs against the same target or with similar mechanisms, relevant knockout animal model results, and any clinical signals from related agents. Show that any expected target-related toxicities (e.g. immune activation, on-target toxicity) are already captured.
4. **Design Minimum Essential Studies:** Plan the core animal study in the chosen species to capture general systemic toxicity and PK exposure. This might be separate 1- and 3-month studies in one species, or, as the draft guidance allows, 3-month studies conducted early in development in lieu of separate 1-month and 3-month studies. Ensure that dose levels and duration meet regulatory expectations for the proposed indication and duration of use.

- Use refined study designs to minimize animals *within* the chosen species (e.g. sentinel cohorts, telemetry to reduce group sizes, blood/tissue sampling without necropsy).
- Include sensitive safety pharmacology endpoints in the chosen species as needed, since a second species is absent.

5. **Develop a Weight-of-Evidence Memorandum:** Prepare a formal WoE risk assessment summary. Clearly outline the composition of the WoE:

- *In vitro/NAM Data:* e.g. next-gen assays demonstrating key toxicological endpoints (cytokine release, carcinogenicity signals, hERG channel effects, etc.).
- *Existing in vivo data:* including any pivotal animal studies already done (even if short-term or discovery studies), and what they show.
- *Comparative data:* Data from drugs with the same target or payload (if ADC) – mention any shared adverse effects.

- *Mechanistic understanding:* Discussion of how the drug works (e.g. mode of T-cell engagement) and why certain risks are expected or not expected.
- *Human data, if any:* If an IND follows an initial safety trial, incorporate any human PK/PD or emergent safety information.
- *NAM/Modeling:* Present relevant computational toxicology predictions or organ-on-chip findings, citing any validation references.

This memo should state “based on all of the above evidence, the proposed reduced nonclinical program provides adequate safety cover for initial human testing” (for IND) or future clinical phases (for later submissions).

6. **Justify Study Reductions:** In written justification, explicitly map the guidance language to the plan. For example: “Because Drug X does not bind rodent tissues, no rodent toxicology study is proposed (in line with FDA’s guidance that testing is unnecessary where there is no binding (www.globenewswire.com)). We will conduct a single 4-week monkey study with detailed hematologic monitoring, covering potential on-target effects. Weight-of-evidence data (see attached) will address the expected longer-term immune-related toxicity, in lieu of a 13-week study.” When removing any standard study, clearly explain why the risk is low based on collected evidence.
7. **Plan for NAM Integration:** If using NAMs, sponsors should identify or develop in vitro or in silico tools relevant to the drug’s safety profile. For example, humanized organ system assays for target organs (liver spheroids for hepatotoxic payloads, neurotoxicity chip for CD3-related CNS risk, etc.). Sponsors proposing NAM-based strategies should discuss them with FDA early.
8. **Document Assurances for FDA:** Even with reduced animal work, FDA will still expect assurance of safety to enter first-in-human trials. So sponsors must maintain rigor: GLP compliance for any pivotal study, thorough pharmacodynamic and toxicokinetic analysis, and validated endpoints. The guidance is not a loophole to skip due diligence, but rather permission to optimize it.
9. **Provide “Nonkill” Endpoints if Possible:** The guidance suggests that sponsors can design studies “that do not require ending an animal’s life” if scientifically valid (xtalks.com). This could mean using serial biopsies or imaging in lieu of terminal pathology in some cases. While aggressive, such refinements align with the spirit of 3Rs and should be mentioned if feasible.

Following these steps, a sponsor can prepare a well-justified nonclinical proposal that aims to address FDA’s questions while minimizing unnecessary animal use. The draft guidance is non-binding, and the FDA review division makes the final determination on whether any proposed program is sufficient. In any submission or meeting request, citing the guidance document and related FDA statements (e.g. Press Release (www.fda.gov) and Year One Roadmap report (www.fda.gov)) will bolster the proposal.

Data Analysis and Evidence

To underpin these recommendations, it is instructive to review some quantitative and empirical data:

- **Drug Attrition:** As noted, *>90% of animal-safe drugs fail in humans* (www.fda.gov). This statistic from FDA's press release (citing the roadmap report) underscores the inefficiency of relying solely on animal models. It suggests that a paradigm prioritizing human-relevant data (woe/NAM) could better sift promising candidates.
- **Development Time:** The FDA press release frames the guidance as part of a larger effort to shorten development. It reminds us that bringing a drug from discovery to market is often **10–12 years** (www.globenewswire.com). Reducing nonclinical study duration (via one species or skipping studies) can shave months or years, especially since 3-month primate studies alone add substantial time. This benefit is echoed by FDA's commissioner: speeding up approvals and driving down costs (www.globenewswire.com) (www.fda.gov).
- **Animal Use Reduction:** While exact counts depend on many factors, some illustrative figures exist. For example, releasing updated guidance on bacterial endotoxin testing (via recombinant products) could save *over 1 million horseshoe crabs per year* (www.fda.gov). Although not directly linked to oncology biologics, it highlights the scale of conservation impact. The FDA notes as a goal that "thousands of animals, including dogs and primates, could eventually be spared each year" by these initiatives (www.fda.gov). Sponsors citing these figures can reinforce the ethical imperative.
- **Case Examples:** The drugs examined above (Opdivo, Bavencio, T-DM1) reflect real practice. For instance, T-DM1's safety paper (www.sciencedirect.com) shows how well-behaved conjugates can be: at high doses it was *"well tolerated"* and toxicities mirrored DM1's known profile (www.sciencedirect.com). Where effects are well documented, sponsors can emphasize congruence between animal and human risk, rather than performing *new* animals tests to discover obvious outcomes.

Taken together, the evidence supports that a focused, risk-based approach can maintain safety. Agencies themselves project that moving to advanced methods will "improve prediction of safety, accelerate development timelines, reduce costs, and expand patient access" (www.fda.gov). In other words, there is regulatory intent and stakeholder consensus that the benefits outweigh the risks of reducing animal studies in these contexts.

International and Ethical Perspectives

The FDA's initiative does not occur in isolation. Globally, regulators are recalibrating animal use in drug development:

- **FDA Animal Testing Roadmap:** The FDA's April 2025 announcement described a partnership with ICCVAM to speed validation of new methods and a pilot program for select monoclonal antibody developers, and said FDA would begin using pre-existing real-world safety data from other countries with comparable regulatory standards. The oncology biologics guidance is one further step in that effort.
- **EMA and EU:** The EMA's Innovation Task Force (ITF) gives developers an opportunity to discuss 3R-compliant methods, and publicly champions moving away from animal tests (www.ema.europa.eu). Though a specific EMA guideline like this draft does not yet exist for oncology biologics, EMA guidelines

often defer to ICH on tech safety, and may update S6 in future.

- **UK/MHRA:** Even outside the EU, the UK's MHRA has published explicit support for non-animal approaches (www.gov.uk). Its guidance emphasizes 3Rs and individual case assessment. It states that "exceptions to international guidelines have always been acceptable, in principle" when justified (www.gov.uk). This aligns closely with the FDA's approach of case-by-case waivers via WoE.
- **Ethical Imperative:** From an ethical viewpoint, these changes reflect society's increasing discomfort with animal testing when alternatives exist. The FDA roadmap frequently mentioned *ethics* and *patient benefit*. In the April 2025 FDA release, Commissioner Makary said, "It is a win-win for public health and ethics" (www.fda.gov). Academic ethicists note that replacing low-value animal tests with human-based data respects animal welfare without compromising human safety (if done responsibly) (www.ema.europa.eu). The EMA's statement about reducing suffering in animals (e.g. horseshoe crabs) parallels the sentiment across agencies. Sponsors often have internal 3Rs obligations; aligning with the draft guidance helps companies fulfill corporate social responsibility to animal welfare, which can be a reputational benefit.
- **Dissenting Views:** Some experts caution that weight-of-evidence approaches require high-level expertise and risk missing unknown toxicities. For emerging modalities (bispecifics, ADCs) with few precedents, there may be worry that skipping studies could miss rare events. The guidance acknowledges residual risk: it says FDA will evaluate whether the WoE "sufficiently addresses safety risks" (www.lachmanconsultants.com). Thus, sponsors should not expect blanket approval of any shortcut; going into meetings, they should present both potential uncertainties and mitigation plans (e.g. voluntary post-marketing surveillance commitments).

Overall, the movement is toward harmonized global acceptance of reduced animal testing. Companies developing products internationally will benefit from consistent approaches: in the U.S., EU, UK, and Japan, the trend is clear that rigid two-species requirements are easing for biologics when justified by data. It remains important for sponsors to track not just FDA guidance but also evolving ICH/EMA positions (for example, watch for ICH S6(R3) discussions).

Implications and Future Directions

The draft guidance has far-reaching implications:

- **For Drug Sponsors:** Companies can **save time and cost** by eliminating unnecessary animal studies. Conducting fewer large animal studies reduces expenses (monkey studies can cost millions each) and can accelerate planning (less in-study data to wait for). Streamlining toxicology may shorten the pre-IND timeline and enable quicker first-in-human trials, especially critical in oncology where unmet need is high. It can also improve predictions: reliance on human-relevant data might avoid wasted clinical trials due to animal-only findings. From a quality standpoint, sponsors must beef up their data integration and risk analysis skills – teams of toxicologists will need to be adept at WoE thinking. Regulatory

submissions will be more narrative-centric than data-checklist-centric. Some organizations are already preparing: pre-IND/ITF meetings to vet NAMs and WoE plans will become a standard step in development plans for new biologics or ADCs.

- **For Regulators:** FDA reviewers must adapt to evaluating unconventional datasets. The guidance already signals that reviewers in CDER's oncology divisions will assess WoE submissions, implying they will consider in vitro, computational, and literature data as evidence. Regulatory staff training in NAMs and risk assessment will be needed. We may see formal guidance on how to format WoE assessments (possibly as appendices to IND modules). In addition, FDA may publish case studies or FAQs summarizing how past companies successfully implemented WoE. Interagency and international alignment is likely, given the global roadmap goals (www.fda.gov).
- **For Patients and Society:** By accelerating drug development, patients may gain earlier access to novel cancer therapies without waiting for lengthy nonclinical cycles. In the big picture, the FDA explicitly tied this guidance to that benefit (www.globenewswire.com) (www.fda.gov). The reduction in animal use — thousands of primates, dogs, and other species spared — also aligns with societal values around animal welfare. It may inspire greater public trust that drug evaluation is at the cutting edge of science. However, patients must be assured that no safety compromise occurs; thorough communication about how human-relevant data might even improve safety prediction will be necessary by both FDA and sponsors.
- **For the Field of Biotechnology:** This guidance is part of a broader **cultural and technological shift**. We expect to see rapid growth in investment for NAM technologies and computational toxicology applied in oncology. Pharmaceutical research may increasingly collaborate with academic/on-chip developers. The guidance could inadvertently raise the bar for first-in-human safety: sponsors will need to demonstrate more human-relevant evidence, which could be challenging for small companies without NAM capabilities. Conversely, it opens opportunities for innovators (e.g. companies developing organoid tests) to participate in pharmaceutical pipelines. In academia, publications on organoid toxicology of oncology drugs will gain prominence as they are directly relevant to regulatory submissions.
- **Challenges:** The long-term implications also include potential pitfalls. If poorly executed, a woefully thin WoE could lead to unforeseen adverse events in clinical trials. The regulatory expectation is still that human trials begin only when adequately safe. The occasional pushback (e.g. from advisory committees concerned with novel toxicities) could result in the FDA tightening requirements for certain modalities. Vigilance in post-marketing surveillance and communication will be crucial.

Looking ahead, we anticipate:

- Finalization of the guidance later in 2026, likely with minor adjustments based on comments.
- Continued expansion of similar guidances to other therapeutic areas (FDA has signaled interest in rolling out more streamlined safety guidances, e.g. the Dec 2025 mAb guidance (www.fda.gov) is one step; others may focus on other biologics like cytokines or gene therapies).
- Eventually, true **quantitative–systems toxicology** models may allow sponsors to fully simulate human risk, potentially enabling human trials with minimal in vivo studies. In the author's speculative view, the default expectation for many biologics could shift by 2030 to designing first-in-human programs based

on validated NAM data and WoE alone.

Conclusion

The May 2026 FDA draft guidance on **Streamlined Nonclinical Safety Studies for Oncology Biologics, ADCs, PD-(L)1, and CD3 Bispecifics** marks a transformative policy that both reflects and accelerates the evolution of drug development science. It codifies what sponsors have increasingly practiced in an ad hoc way: trusting one relevant species and a comprehensive evidence base to assure safety, rather than literal two-animal species conformity. The guidance is a culmination of the FDA's Roadmap to reduce animal testing (www.globenewswire.com) (www.fda.gov) and the broader global movement toward human-relevant methods.

This report has dissected the guidance's provisions, combining official text with historical data and practical examples. We have described how PD-1 inhibitors, bispecific T-cell engagers, ADCs, and general oncology biologics can all fit within the new paradigm. We have also discussed how sponsors should now deliberately plan streamlined programs, using weight-of-evidence to justify reduced animal use. Key to success will be thorough preparation of WoE dossiers, early FDA engagement, and employing NAMs where possible to bolster confidence (www.globenewswire.com) (www.fda.gov).

For sponsors, aligning with this guidance means fewer primates and rodents euthanized, lower development costs, and potentially faster progress through clinical trials. It also means investing effort in data analysis and innovative tools. Regulators, for their part, are betting that these new methods maintain patient safety while ultimately accelerating delivery of novel therapies.

In conclusion, the FDA's draft guidance is a milestone in regulatory science: it invites all stakeholders to participate in a more efficient and ethical approach to evaluating cancer drugs. By following the sponsor playbook herein – integrating all evidence sources, leveraging modern technology, and transparently justifying study designs – developers can be at the forefront of innovation. As all parties move forward, ongoing dialogue, case studies, and post-implementation reviews will refine the approach. The future of oncology drug safety looks to be less about counting animals and more about counting on robust science.

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