U.S. FOOD & DRUG ADMINISTRATION

Reducing Animal Testing in Nonclinical Studies

Year One Progress and the Path Forward

APRIL 2026

Executive Summary

In April 2025, the FDA released its *Roadmap to Reducing Animal Testing in Preclinical Safety Studies*, outlining a strategy to modernize drug development. One year later, that vision has translated into measurable progress that is already saving lives—both human and animal.

This transformation rests on concrete achievements: new policies that eliminated unnecessary six-month primate studies for monoclonal antibodies; expanded weight-of-evidence approaches that can replace entire carcinogenicity studies requiring over 1,000 animals per product; the first AI-based drug development tool qualified for regulatory use; a searchable database providing clarity on where alternative methods are acceptable; formalized international regulatory alignment; and a permanent pathway for qualifying innovative methods with more than 16 active submissions.

This is regulatory science in action: systematic, evidence-based transformation that protects patients, respects animal welfare, and harnesses 21st-century innovation to make drug development faster, more cost-effective, and more predictive of human outcomes. While meaningful progress has been made, significant work remains. This report outlines both what has been achieved and the steps needed to continue advancing this transition.

Introduction

The Scientific Imperative: When Animal Models Fail Patients

For decades, drug development has relied on animal testing to assess safety before initiating human trials. While these studies can predict certain toxicities, their ability to fully anticipate human responses is limited by differences in disease state, target biology, pharmacokinetics, metabolism, and idiosyncratic or off-target responses between species. As a result, over 90% of drugs that appear safe in animals fail to receive FDA approval, predominantly due to safety and/or efficacy issues that only become apparent in human trials.[1] This translational gap delays patient access to meaningful therapies, increases costs, and introduces avoidable safety risk.

Scientific advances now offer a better path forward. Weight-of-Evidence risk assessments and New Approach Methodologies (NAMs)—including human organ-on-chip systems, computational modeling, artificial intelligence (AI), and advanced in vitro assays—can provide more accurate, human-relevant insights into drug effects. These tools can improve prediction of toxicity, immunogenicity, and pharmacokinetics while reducing reliance on animal studies.

While animal models have proven particularly inadequate for common diseases, studies also show poor predictive value for cancer therapeutics[2], Alzheimer's disease treatments[3], and

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[1] Marshall LJ, Bailey J, Cassotta M, Herrmann K, Pistollato F. Poor Translatability of Biomedical Research Using Animals - A Narrative Review. *Altern Lab Anim*. 2023 Mar;51(2):102-135. doi: 10.1177/02611929231157756. Epub 2023 Mar 7. PMID: 36883244.

[2] Mak IW, Evaniew N, Ghert M. Lost in translation: animal models and clinical trials in cancer treatment. *Am J Transl Res*. 2014 Jan 15;6(2):114-8. PMID: 24489990; PMCID: PMC3902221.

[3] Pippin JJ, Cavanaugh SE, Pistollato F, Grignard E, Mendoza J, Briel M. Animal Research for Alzheimer Disease: Failures of Science and Ethics. In: Herrmann K, Jayne K, editors. *Animal Experimentation: Working Towards a Paradigm Change*. Vol. 22. Leiden: Brill; 2019. p. 480-516. Available from: http://www.jstor.org/stable/10.1163/j.ctvjhzq0f.27

inflammatory disease interventions.[4] The genomic responses in mouse models of inflammatory diseases, for instance, poorly mimic human responses according to research published in the *Proceedings of the National Academy of Sciences*.[4]

The consequences extend beyond scientific accuracy to patient safety. The TGN1412 tragedy exemplifies the dangers: this monoclonal antibody, designed to treat autoimmune diseases and leukemia, underwent extensive preclinical testing in monkeys at doses up to 500 times higher than the planned human dose, with no adverse effects observed.[5] Yet within minutes of administration to six healthy human volunteers in a 2006 Phase I trial, all experienced catastrophic immune system activation—life-threatening cytokine release syndrome that caused multiple organ failure, with some participants requiring intensive care for months. The disconnect was biological: the antibody's target (CD28) functions differently in humans than in monkeys, a difference animal testing could not reveal. That disaster fundamentally changed how drugs are tested, leading to development of laboratory tests using actual human blood and immune cells that can now predict these dangerous immune reactions—demonstrating that human-based methods can be more accurate than animal studies for certain safety assessments.

The Economic and Ethical Imperative: The True Cost of Outdated Models

Economic and practical challenges compound these scientific limitations. Developing a monoclonal antibody costs $650-$750 million and takes up to 9 years, with typical programs using 144 non-human primates at costs now reaching $50,000 per animal.[6,7] The time and expense of long-term animal studies delay therapies reaching patients, while the majority of development failures occur because issues were not evident in animal tests.

Beyond traditional laboratory animals, over one million horseshoe crabs are harvested annually for bacterial endotoxin testing reagents, raising conservation concerns for these ancient marine animals.[8] The stress of laboratory life itself can impact immune function, inflammatory responses, metabolism, and disease susceptibility in research animals, potentially confounding the very data these studies aim to generate.[9]

The Opportunity for Scientific and Policy Alignment

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[4] Seok J, Warren HS, Cuenca AG, et al; Inflammation and Host Response to Injury, Large Scale Collaborative Research Program. Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc Natl Acad Sci U S A*. 2013 Feb 26;110(9):3507-12. doi: 10.1073/pnas.1222878110. Epub 2013 Feb 11. PMID: 23401516; PMCID: PMC3587220.

[5] Vessillier S, Eastwood D, Fox B, Sathish J, Sethu S, Dougall T, Thorpe SJ, Thorpe R, Stebbings R. Cytokine release assays for the prediction of therapeutic mAb safety in first-in man trials--Whole blood cytokine release assays are poorly predictive for TGN1412 cytokine storm. *J Immunol Methods.* 2015 Sep;424:43-52. doi: 10.1016/j.jim.2015.04.020. Epub 2015 May 7. PMID: 25960173; PMCID: PMC4768082.

[6] Chapman K, Pullen N, Coney L, Dempster M, Andrews L, Bajramovic J, Baldrick P, Buckley L, Jacobs A, Hale G, Green C, Ragan I, Robinson V. Preclinical development of monoclonal antibodies: considerations for the use of non-human primates. *MAbs*. 2009 Sep-Oct;1(5):505-16. doi: 10.4161/mabs.1.5.9676. Epub 2009 Sep 30. PMID: 20065651; PMCID: PMC2759500.

[7] https://emulatebio.com/organ-chips-vs-nhps-cost-calculator/

[8] Atlantic-States-Marine-Fisheries-Commission. "Horseshoe Crab - Atlantic States Marine Fisheries Commission: Species Information." Retrieved 3/30/2026, from https://asmfc.org/species/horseshoe-crab/.

[9] Bailey J. Does the stress of laboratory life and experimentation on animals adversely affect research data? A critical review. *Altern Lab Anim.* 2018 Sep;46(5):291-305. doi: 10.1177/026119291804600501. PMID: 30256135.

Recognizing this convergence of scientific capability, policy support, and public demand, FDA published its Roadmap on April 10, 2025. The Roadmap began with monoclonal antibodies as a promising initial focus area, with plans to expand to other biological molecules, new chemical entities, and medical countermeasures. It outlined specific implementation steps for the first three years, long-term goals for making animal studies the exception rather than the norm, and a framework for interagency coordination through the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM).

How the Agency Turned a Bold Vision into Concrete Progress on Reducing Animal Testing

One year ago, FDA's Roadmap made specific, measurable commitments to transform drug development. The Roadmap identified critical implementation steps across several domains: leveraging existing international data, encouraging sponsor engagement with alternative methods, developing databases and repositories, reducing routine animal testing, establishing validation pathways, creating regulatory guidance, building internal capacity, and coordinating across agencies and international partners. This report is an accountability document showing how we have delivered on those promises.

Table 1 below shows each Roadmap commitment, our progress status, and the impact achieved. In several areas, we exceeded our initial goals. In others, we have built the foundation that will enable accelerated progress in years two and three. Importantly, these achievements are not isolated initiatives but interconnected elements of a systematic transformation. Each validation framework supports multiple guidance documents, each international partnership multiplies the impact of domestic policy, and each qualified alternative method creates precedent for the next.

Table 1: Assessment of 2025 Roadmap Goals

Roadmap Goal	Status	Impact
Explore Pre-existing International Data	**Achieved**	Aligned international strategies and established foundation for global data sharing to inform regulatory decisions
Encourage Sponsors to Submit NAM Data in Parallel	**Exceeded**	Removed regulatory uncertainty and created a transparent pathway for sponsors to confidently submit alternative methods
Develop Open-Access Repository of Toxicity Data	**Achieved**	Foundation established for comprehensive database; ongoing development toward full vision
Reduce Routine 6-Month Primate Testing for Monoclonal Antibodies (mAb)	**Achieved**	Will save hundreds of non-human primates annually while maintaining safety standards
Establish Validation and Qualification Pathways	**Achieved**	Clear, actionable framework transforms abstract question of "when is an alternative acceptable?" into concrete requirements
Develop Regulatory Guidance and Standards	**Exceeded**	Promulgation of FDA's current thinking via regulatory guidance documents
Training, Communication, and Culture Change	**Achieved**	NAMs expertise embedded across the agency through organizational infrastructure and cultural transformation
Interagency Coordination	**Achieved**	Federal partnership operationalized; coordination extends beyond U.S. agencies to international regulatory community

In the twelve months since the Roadmap was published, that vision has been translated into action. Highlights include international regulatory alignment, guidance expected to save hundreds of non-human primates (NHPs) annually, and qualification of the agency's first AI-based drug-development tool. Together, these efforts are making reduced animal testing an achievable reality rather than an aspirational goal.

The accomplishments span four critical domains: building foundational infrastructure and frameworks that enable sustainable change; creating transparency and certainty that remove barriers to adoption; delivering immediate impact through guidance and qualified tools that are saving animals now; and multiplying impact through international alignment. Table 2 summarizes these key accomplishments, their timing, and their quantifiable impact.

Table 2: Summary of Key Accomplishments (April 2025 - March 2026)

Initiative	Date	Accomplishments
International Regulatory Workshop	July 2025	Global alignment on NAMs strategies
Innovative Science and Technology Approaches for New Drugs (ISTAND) Program Becomes Permanent	July 2025	16+ active submissions; clear qualification pathway of drug development tools
NIH-FDA Partnership (MOU)	August 2025	Aligned research and regulatory infrastructure
Liver-on-Chip Protocol Publication	November 2025	Validated technical protocols for adoption
Monoclonal Antibody Guidance	December 2025	Reduced/eliminated 6-month NHP studies
First AI Tool Qualified (AIM-NASH)	December 2025	Proof of concept for AI in drug development
NAMs Acceptability Database	December 2025	Transparency on acceptable alternatives
15-Year NAMs Analysis Published	December 2025	Evidence-based prioritization (93% in silico/in vitro)
Pyrogen and Endotoxins Testing: Questions and Answers	March 2026	Transition to recombinant endotoxin reagents
General NAMs Validation Framework	March 2026	Human-centric methods as regulatory default

Building the Foundation: Infrastructure and Frameworks That Enable Change

FDA Establishes Cross-Center Infrastructure to Coordinate Alternative Methods Expertise

Throughout 2025, FDA built the internal infrastructure necessary to sustain progress on alternative methods. The effort began in April 2025 when the Center for Drug Evaluation and Research (CDER) established a NAMs Coordinating Committee to align efforts across the center. Both CDER and the Center for Biologics Evaluation and Research (CBER) now encourage sponsors to discuss NAMs early in development through Initial Targeted Engagement for Regulatory Advice on CBER/CDER Products (INTERACT), Critical Path Innovation Meetings, and other pre-submission meetings.

Building on this foundation, FDA established a core NAMs workgroup in January 2026, bringing together subject matter experts from across the agency. Most ambitiously, CDER developed a concept of operations for a NAMs Integrated Review Team (NAMs-IRT) to be piloted in 2026. The NAMs-IRT will provide a centralized, cross-disciplinary review framework to evaluate and integrate alternative methods into drug development and regulatory decision-making.

This organizational infrastructure is essential because NAMs rarely fit neatly into traditional review divisions organized by therapeutic area or product type. A computational toxicology model might be relevant across oncology, cardiology, and neurology. An organoid system might inform both efficacy and safety assessments. Integrated review teams and cross-center workgroups ensure that expertise is shared, best practices are disseminated, and evaluation approaches remain consistent across the agency.

NIH-FDA Partnership Formalizes Collaboration to Accelerate Human-Relevant Testing Methods

On August 27, 2025, FDA and NIH formalized a partnership that combines the nation's premier biomedical research capabilities with regulatory expertise. Memorandum of Understanding (MOU) 225-25-012 established the framework for collaboration through the Complement Animal Research In Experimentation (Complement-ARIE) Program, creating an ecosystem designed to accelerate the standardization, qualification, and adoption of human-relevant alternative methods.

The partnership leverages NIH's technology development centers, data infrastructure, and validation and qualification networks—resources that have driven biomedical breakthroughs for decades—and aligns them with FDA's regulatory science priorities. Instead of researchers developing promising technologies in isolation, wondering whether FDA will accept them, the MOU creates a collaborative framework where development and regulatory thinking advance together. This alignment is critical because the best alternative method in the world has no impact if developers lack confidence that regulators will accept it.

ISTAND Pilot Becomes Permanent Program, Opening Opportunities for Alternative Method Qualification

On July 31, 2025, FDA made the Innovative Science and Technology Approaches for New Drugs (ISTAND) pilot program permanent. The program employs the Drug Development Tool (DDT) Qualification regulatory framework, providing a clear, predictable pathway for developers to gain formal FDA acceptance of NAMs.

For the latest ISTAND submissions, see CDER & CBER Drug Development Tool Qualification Project Search:

https://force-dsc.my.site.com/ddt/s/

During its pilot phase, ISTAND accepted eight novel submissions, a remarkable achievement that demonstrated both industry appetite for alternatives and FDA's capacity to evaluate them rigorously. Since becoming permanent, innovation has accelerated. The program now has over 16 active submissions at various qualification stages (as of early 2026), signaling that FDA has established infrastructure to systematically evaluate and adopt alternatives.

Current submissions demonstrate the breadth of innovation: a liver Microphysiological System (MPS) has advanced to final qualification stages; six letters of intent have been submitted for

additional liver MPS applications including dosing optimization in liver disease trials; developers are pursuing MPS platforms for clinical drug-induced liver injury (DILI) risk assessment and hepatotoxicity quantification; human kidney chips are being developed to assess nephrotoxicity; a chorio-decidual organ-on-chip is in development for developmental and reproductive toxicity risk reduction; and an iPSC-cardiomyocyte system is being created to predict arrhythmia risk.

FDA Publishes Comprehensive Validation Framework, Declaring Human-Centric Methods the New Regulatory Default

On March 18, 2026, FDA published a draft guidance document that represents perhaps the most important milestone in the regulatory infrastructure envisioned in the Roadmap. *General Considerations for the Use of New Approach Methodologies* establishes four core validation principles that transform the abstract question of "when is an alternative acceptable?" into concrete, actionable requirements.

The draft guidance provides clarity developers have long sought through four foundational principles:

- *Context of Use:* clear definition of regulatory purpose
- *Human Biological Relevance*: demonstration of how methods assess toxicity
- *Technical Characterization*: establishment of scientific confidence through robust protocols
- *Fit-for-Purpose*: assurance methods support regulatory decision-making

These principles create a Roadmap to regulatory acceptance. A developer proposing an organ-on-chip system or computational model now has explicit criteria against which to design validation studies. Reviewers have consistent standards for evaluation. The framework shifts the burden from “prove this alternative is acceptable” to “demonstrate this method meets established validation principles,” a subtle but significant change that positions human-relevant methods as the default rather than the exception.

Creating Transparency and Certainty: Removing Barriers to Adoption

FDA Launches Searchable Database Showing Exactly Where Alternative Methods Are Acceptable

The *CDER/Office of New Drugs Streamlined Nonclinical Studies and Acceptable New Approach Methodologies (NAMs)* database went live in October 2025, providing a searchable, regularly updated inventory of specific drug development contexts where streamlined nonclinical programs are acceptable. With this, FDA eliminated one of the biggest barriers to adopting alternative methods and streamlined approaches for nonclinical testing: uncertainty about what the agency will accept.

Instead of designing animal studies based on decades-old assumptions about what FDA requires, drug developers can search for their specific development context and see exactly where reduced sample sizes, fewer species, or alternative methods have been accepted. The database spans a variety of therapeutic areas safety endpoints, transforming institutional knowledge that previously only existed in reviewers’ experience into accessible guidance.

The impact extends beyond individual development programs. By making acceptance criteria transparent, the database creates positive feedback loops: developers gain confidence to propose alternatives, successful applications are documented, and future developers can build on that precedent. Regulatory uncertainty, once a major impediment, becomes regulatory clarity.

FDA Publishes Comprehensive Analysis of 15 Years of Alternative Method Submissions

In December 2025, FDA published *A CDER Perspective: Landscape of New Approach Methodologies (NAMs) Submitted in Drug Development Programs*, a comprehensive analysis of 15 years of alternative method submissions that revealed a striking pattern: 93% of submitted NAMs are either in silico (49%) or in vitro (44%) methods.[10]

The analysis provides strategic focus: those are the areas where FDA's validation infrastructure, guidance development, and expertise building will have maximum impact. Rather than spreading resources thinly across all possible alternative approaches, FDA can concentrate on the methods developers are actually proposing and where the greatest near-term impact is achievable.

FDA also analyzed its own experience systematically to identify trends, gaps, and opportunities at the reviewer level in a November 2025 article.[11] This manuscript demonstrated how FDA/CDER has incorporated NAMs into standard nonclinical assessments and described how specific tests became validated and internationally accepted alternatives to animal testing for regulatory decision-making.

FDA Researchers Publish Suggestions for Optimizing and Characterizing Liver-on-a-Chip Systems

In November 2025, FDA researchers from the National Center for Toxicological Research (NCTR) and Center for Drug Evaluation and Research (CDER), collaborating with Emulate Inc. and the University of North Carolina at Chapel Hill, published *Challenges and solutions in measuring commonly used biomarkers for drug-induced liver injury in a liver-on-a-chip platform*.[12]

The publication systematically identified specific assay challenges in liver MPS and provided suggestions for establishing reliable, reproducible protocols for translational DILI biomarkers. Liver-on-a-chip systems hold enormous promise for predicting human liver toxicity, which is a major cause of drug development failures and post-market withdrawals.[13] However, promise only becomes reality when researchers solve the technical challenges of measurement, standardization, and reproducibility.

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[10] Dao T, Sadrieh N. A CDER perspective: landscape of new approach methodologies (NAMs) submitted in drug development programs. *Regul Toxicol Pharmacol.* 2026;165:106007. doi:10.1016/j.yrtph.2025.106007.

[11] Yao J, Peretz J, Bebenek I, et al. FDA/CDER/OND experience with new approach methodologies (NAMs). *Int J Toxicol.* 2026;45(2):136-156. doi:10.1177/10915818251384270.

[12] Shi Q, Schnackenberg LK, Ren L, Papineau KS, Oliphant JJH, Avigan MI, et al. Challenges and solutions in measuring commonly used biomarkers for drug-induced liver injury in a liver-on-a-chip platform. *Toxicol Lett*. 2025;413:111735. doi:10.1016/j.toxlet.2025.111735.

[13] Drug-induced liver injury (DILI): Current status and future directions for drug development and the post-market setting. A consensus by a CIOMS Working Group. *Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS)*; 2020. doi: 10.56759/ojsg8296.

When drug developers consider using liver-on-a-chip systems, they can now reference these suggestions, increasing confidence that their data will be interpretable and acceptable to regulators. This type of technical guidance—granular, practical, and grounded in FDA's own research—accelerates adoption by reducing the trial-and-error phase that often accompanies novel methods.

Delivering Immediate Impact: Guidance and Applications Saving Animals Now

Monoclonal Antibody Guidance Reduces 6-Month Primate Studies, Saving Hundreds of Animals Annually

On December 2, 2025, FDA released draft guidance titled *Monoclonal Antibodies: Streamlined Nonclinical Safety Studies*. For decades, developing mAbs in non-oncology indications meant subjecting NHPs to six months of toxicology testing. The new guidance changes the equation: 6-month studies are not needed when 3-month studies are supplemented with a weight-of-evidence risk assessment. The risk assessment could include NAMs, as appropriate. In some cases, NHP testing can be eliminated entirely or be limited to a short-term study. Beyond ethical considerations, individual NHPs may cost up to $50,000, substantially increasing the cost of drug development. Reducing NHP use therefore represents a significant near-term benefit for patients, developers, and animal welfare.

The guidance also demonstrates FDA's weight-of-evidence approach in action. Rather than requiring a single alternative method to perfectly replicate an animal study, the agency accepts that multiple sources of evidence—including shorter-duration studies, in vitro data, human-relevant assays, and computational models—can collectively provide adequate safety assurance.

FDA Qualifies First Artificial Intelligence Tool for Drug Development, Ushering in New Era

On December 8, 2025, FDA crossed a technological threshold by qualifying AIM-NASH, its first AI-based drug development tool for use in metabolic dysfunction-associated steatohepatitis (MASH) clinical trials. AIM-NASH addresses a persistent challenge in liver disease research by reducing variability and time required for pathologists to score liver biopsy components. By enabling AI-assisted scoring, the tool is one step towards more efficient and reliable clinical trials.

FDA Advances Guidance to Replace Horseshoe Crab Testing with Recombinant Alternatives

Released on March 18, 2026, FDA's Level 2 update to "Pyrogen and Endotoxins Testing: Questions and Answers" guidance addresses an often-overlooked category of animal welfare: the harvesting of horseshoe crabs for production of Limulus Amoebocyte Lysate (LAL) reagent used in bacterial endotoxin testing. Horseshoe crabs are harvested by the hundreds of thousands annually, and their blood is extracted for LAL reagents. While most survive the process, the practice raises both conservation and animal welfare concerns.

The updated guidance provides flexibility for manufacturers to transition from the LAL reagents to recombinant reagents. Available data shows that the recombinant reagents deliver equivalent performance without the harvesting and use of marine animals. The transition to use of recombinant reagents for bacterial endotoxin testing also demonstrates how alternatives can address multiple concerns simultaneously—animal welfare, supply chain resilience, and environmental conservation.

Multiplying Impact Through International Alignment

International Regulators Align Strategies at FDA-NIH Workshop on Reducing Animal Testing

On July 7, 2025, FDA and NIH convened a workshop titled *Reducing Animal Testing,* which brought together federal partners and international regulators from the European Medicines Agency (EMA), Germany's Federal Institute for Risk Assessment (BfR), Japan's Pharmaceuticals and Medical Devices Agency (PMDA), and Australia's Therapeutic Goods Administration (TGA).

The workshop addressed the fundamental reality that regulatory requirements must be harmonized to maximize impact. Participants shared successes, aligned on innovations in AI and computational toxicology, and coordinated implementation strategies. When major regulatory authorities move in concert, the impact multiplies exponentially.

The workshop was not merely an information-sharing exercise but helped in building the international consensus that will make alternatives the global standard. A developer who knows that FDA, EMA, PMDA, and TGA all accept weight-of-evidence approaches for monoclonal antibodies can confidently design streamlined programs. Without that alignment, even the most progressive guidance from a single agency has limited impact because developers must still satisfy the most conservative regulatory requirements in their target markets.

Next Steps

The Roadmap's ultimate vision was to make animal studies the exception rather than the rule for nonclinical safety testing, with a comprehensive integrated NAM toolbox becoming the new standard. The first year's achievements represent a benefit to all stakeholders: patients gain access to safer, more effective therapies developed through human-relevant testing methods; animals are spared from testing with hundreds of NHPs and over one million horseshoe crabs saved annually; and industry benefits from reduced costs, shorter timelines (potentially reducing the 9-year average for mAb development), and decreased regulatory uncertainty. The foundation established in year one will enable accelerated progress in the following high-impact areas.

Expand Reduced Testing Timeframes Beyond Monoclonal Antibodies

The success of streamlined nonclinical studies for monoclonal antibodies provides a model for other drug categories. FDA will extend weight-of-evidence approaches and reduced duration testing to other biological molecules, new chemical entities, and medical countermeasures. Each expansion requires careful scientific evaluation to ensure safety standards are maintained, but the framework is now established.

Implement Comprehensive Metrics and Tracking Systems

To ensure accountability and measure progress, FDA will implement systems to track and quantify changes in animal use across drug development programs. These metrics will enable data-driven decisions about where NAMs are having the greatest impact and where additional guidance or validation work is needed.

Advance Coordinated Validation Efforts for Critical Endpoints

Building on the 15-year analysis showing that 93% of NAMs are in silico or in vitro methods, FDA will prioritize validation efforts for computational and cell-based approaches addressing critical drug development endpoints. This includes expanding validation of organ-on-chip systems, computational toxicology models, and advanced in vitro assays.

Establish Open-Access Repository of Toxicity Data

The Roadmap envisioned a comprehensive international toxicity database that would enable better use of existing data and reduce duplicative testing. Progress has been made in establishing the foundation, but full implementation requires continued development of database governance, data standardization, and international data-sharing agreements.

Comprehensive NAM Toolbox Across All Critical Endpoints

Currently, validated alternatives exist for some endpoints (skin sensitization, mutagenic impurities) but not others (developmental toxicity, chronic toxicity). Systematic validation efforts must expand to cover the full spectrum of safety assessments required for drug approval.

Integration of Multiple NAMs in Weight-of-Evidence Frameworks

The future is not a single alternative method replacing each animal study but rather integrated approaches where multiple NAMs—computational models, in vitro assays, organ-on-chip systems, and human data—collectively provide more comprehensive and human-relevant safety evidence than any single method alone.

Enhance International Regulatory Harmonization

As alternatives become more sophisticated and context-specific, maintaining international alignment becomes both more important and more challenging. Sustained engagement through ICCVAM, ICH (International Council for Harmonization), and bilateral regulatory collaborations will be essential.

Cultural Transformation Across the Drug Development Ecosystem

Regulatory acceptance is necessary but not sufficient. Achieving the vision requires cultural change among developers (confidence in proposing alternatives), reviewers (expertise in evaluating novel methods), researchers (focus on human-relevant models), and the public (understanding that alternatives can provide superior safety evidence).

Conclusion

The Roadmap's vision has translated into measurable impact. Hundreds of non-human primates and over one million horseshoe crabs will be saved annually, with potential for thousands more animals as methods expand. Beyond the numbers, the infrastructure is now in place—permanent qualification pathways, validation frameworks, transparent databases, international alignment, and cross-agency partnerships—to sustain and accelerate this transformation.

The benefits extend across all stakeholders. Patients gain access to safer, more effective therapies developed through human-relevant methods. Industry benefits from reduced costs, shorter timelines, and decreased regulatory uncertainty. Science advances through methods that are more predictive and aligned with modern understanding of human biology. And animals are spared from testing that often fails to translate to human outcomes.

The foundation is built, but the work continues. Success will be measured by the treatments that reach patients faster, the safety issues predicted through human-relevant testing, and the continued progress toward making animal studies the exception rather than the rule.