U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
OFFICE OF THE SECRETARY

FEWER ANIMALS. BETTER DATA. FASTER CURES.

A NEXT-GENERATION STRATEGIC FRAMEWORK TO ACCELERATE MODERNIZATION OF DRUG SAFETY TESTING

TO:	CC:	CC:	DATE:
Secretary Robert F. Kennedy Jr. HHS	**Dr. Marty Makary** FDA Commissioner	**Dr. Tracy Beth Hoeg** Acting CDER Director	**March 21, 2026** STRATEGIC MEMO

EXECUTIVE SUMMARY

Secretary Kennedy, Commissioner Makary, and Acting Director Hoeg:

On March 18, 2026, HHS and FDA achieved a landmark. The FDA released its draft guidance on New Approach Methodologies (NAMs) in drug development — the most comprehensive regulatory framework ever issued for alternatives to animal testing in the United States. Simultaneously, the NIH announced $150 million in Complement-ARIE awards and a new NAMs Data Hub. These actions, combined with the April 2025 Roadmap to Reducing Animal Testing, the December 2025 monoclonal antibody guidance, the $87M organoid center, and the establishment of ORIVA, constitute a genuine paradigm shift.

This memo responds to HHS Press Secretary Emily Hilliard's public invitation for ideas to optimize HHS efforts under Secretary Kennedy's 'Fewer Animals, Better Data, Faster Cures' initiative. It does three things:

- Comprehensively inventories everything already in motion so the full architecture is visible in one place.

- Identifies every gap — scientific, regulatory, legal, and structural — that could slow implementation or expose the effort to legal challenge.
- Proposes 24 specific next-generation innovations and enhancements, none of which require legislation, that would materially accelerate the transition and harden it against challenge.

CORE FINDING: *The March 18 guidance is the right framework. The risk is not that it will be challenged as substantively wrong — it is that implementation will stall without faster validation infrastructure, clearer regulatory incentives, and a proactive legal architecture. This memo addresses all three.*

SECTION I: THE CURRENT ARCHITECTURE — WHAT IS ALREADY IN MOTION

The following is a complete inventory of every major HHS action on NAMs and alternatives to animal testing since January 2025. This is the foundation on which all new proposals in this memo build.

A. FDA Regulatory Actions

1. April 10, 2025 — FDA Roadmap to Reducing Animal Testing in Preclinical Safety Studies

- **WHAT:** The foundational strategic document for the entire initiative. Established a 3-5 year timeline to phase out or reduce animal testing requirements across drug development categories.
- **SIGNIFICANCE:** Signaled FDA's intent to accept NAM data as primary evidence in IND and NDA/BLA submissions.
- **URL:** FDA Phase Out Announcement: fda.gov/news-events/press-announcements/fda-announces-plans-phase-out-animal-testing-requirements-most-drugs-it-regulates
- **DOC:** Roadmap PDF: fda.gov/files/newsroom/published/roadmap_to_reducing_animal_testing_in_preclinical_safety_studies.pdf

2. December 2025 — Draft Guidance on Reducing Non-Human Primate Testing for Monoclonal Antibodies

- **WHAT:** First product-specific guidance explicitly reducing NHP requirements, targeting the largest and most expensive category of biologic drug testing.
- **SIGNIFICANCE:** Established that mAb safety can be assessed using human-relevant immunological models, reducing or eliminating NHP studies for most mAbs.
- **CONTEXT:** Over 100,000 non-human primates are currently held in U.S. research facilities; mAbs are the single largest category driving NHP demand.

3. March 18, 2026 — Draft Guidance: General Considerations for the Use of NAMs in Drug Development

- **DOCKET:** FDA Docket No. FDA-2025-D-6131 | Federal Register: 91 Fed. Reg. 13313-13314 (March 19, 2026)
- **COMMENT PERIOD:** Comments accepted through May 18, 2026 at regulations.gov
- **URL:** URL: fda.gov/news-events/press-announcements/fda-releases-draft-guidance-alternatives-animal-testing-drug-development

The four core validation principles established by this guidance are:

- Context of Use: Clear definition of NAM's intended regulatory purpose
- Human Biological Relevance: Demonstration of how the NAM can assess toxicity in a human-relevant way
- Characterization: Robust description of the NAM's components and operating procedures
- Fit-for-Purpose: Assurance that the NAM assists in regulatory decision-making

KEY INNOVATION IN THIS GUIDANCE: *For the first time, the FDA has clarified that validation and formal qualification are NOT required for a NAM to be submitted in support of a drug application. Sponsors can submit unvalidated NAM data — a major regulatory barrier has been removed.*

4. March 18, 2026 — Level 2 Revision: Pyrogen & Endotoxin Testing Guidance

- **WHAT:** Clarifies transition pathway to recombinant Factor C (rFC) reagents, replacing horseshoe crab-derived Limulus Amebocyte Lysate (LAL) for bacterial endotoxin testing.
- **SIGNIFICANCE:** Aligns with USP Chapter 86 (May 2025). Affects every drug and device regulated by FDA that requires endotoxin testing — one of the highest-volume animal-derived tests in pharmaceutical manufacturing.

B. NIH Actions

5. April 29, 2025 — NIH Establishes ORIVA (Office of Research Innovation, Validation, and Application)

- **WHAT:** First NIH office dedicated solely to coordinating agency-wide NAM development, validation, and scale-up.
- **SIGNIFICANCE:** Serves as hub for interagency coordination and regulatory translation between NIH research and FDA regulatory acceptance.

6. 2025 — NIH $87 Million Center for Organoid Development

- **WHAT:** Dedicated funding center to develop, standardize, and validate organoid platforms for drug testing applications.
- **SIGNIFICANCE:** Fills the critical gap between proof-of-concept organoid research and regulatory-ready, reproducible organoid systems.

7. March 18, 2026 — Complement-ARIE $150 Million Award Announcement

- **WHAT:** First awards under the Complement Animal Research in Experimentation (Complement-ARIE) program.
- **STRUCTURE:** Establishes: Technology Development Centers (TDCs) for cardiac disease, neurological disorders, gynecological diseases, rare diseases, and more; NAMs Data Hub and Coordinating Center (NDHCC) for data sharing and standards; Validation and Qualification Network (VQN) in partnership with the Foundation for the NIH; $7 million NAMs Reduction to Practice Challenge.

- **URL:** NIH press release: nih.gov/news-events/news-releases/nih-invests-150-million-human-based-research-reduce-use-animal-models

8. NIH Policy Shift — Preference for Non-Animal Grant Proposals

- **WHAT:** NIH announced it will no longer fund research projects that rely solely on animal testing, shifting grantmaking preference to proposals incorporating NAMs.
- **SIGNIFICANCE:** Redirects the entire NIH research portfolio — approximately half of the NIH's annual budget currently supports animal use — toward human-relevant science.

C. The Legal Foundation

9. FDA Modernization Act 2.0 (2022) — The Statutory Authority

- **WHAT:** Enacted December 2022. Removed the longstanding statutory requirement that new drugs be tested in animals prior to human trials.
- **LEGAL EFFECT:** Explicitly permits submission of non-animal experimental data as primary evidence for IND, NDA, and BLA applications.
- **SIGNIFICANCE:** The March 18, 2026 guidance explicitly implements this authority, meaning every NAM submission is now backed by a Congressional mandate.

10. MAHA Commission Strategy Report

- **WHAT:** The MAHA Commission's Strategy Report explicitly recommended reducing reliance on animal studies that often fail to replicate complex human conditions.
- **SIGNIFICANCE:** Provides the Executive Branch political and policy authorization for the entire NAM transition initiative.

SECTION II: GAPS, VULNERABILITIES, AND WHAT IS NOT YET BEING DONE

Despite the strong foundation, the following gaps represent where the initiative could stall, be legally challenged, or fail to achieve its full potential. Each gap is paired with a solution in Section III.

Gap 1: The Validation Bottleneck

The March 18 guidance correctly removes the validation requirement as a precondition for NAM submission, but does not yet solve the validation throughput problem. There is no fast-track pathway for NAMs to graduate from 'submitted but unvalidated' to 'validated and widely accepted.' Without that, the same NAMs will be re-reviewed in every application, creating reviewer burden and inconsistent outcomes.

Gap 2: No NAM-Specific Pre-Submission Meeting Protocol

Sponsors are told they can consult their FDA review division when considering NAMs — but there is no structured, standardized pre-IND meeting process specifically designed for NAM data packages. This creates uncertainty and discourages first movers.

Gap 3: Reviewer Capacity and Training

FDA review staff are trained to evaluate animal study data packages. Many have never evaluated an organ-on-chip dataset or an AI-generated PBPK model. The guidance creates the permission structure; it does not yet create the human capital to act on it at scale.

Gap 4: The Data Interoperability Problem

NAM data generated across different platforms (Wyss Liver-Chip vs. Emulate vs. various organoid systems) are not interoperable. There are no universal data standards. This means FDA reviewers cannot systematically compare or aggregate NAM evidence across submissions, limiting the ability to build the cross-sponsor databases needed to validate NAMs at a population level.

Gap 5: Small and Mid-Size Sponsor Access

The most advanced NAMs (multi-organ chips, patient-derived organoids, AI-integrated digital twins) require capital investment, specialized expertise, and infrastructure that large pharmaceutical companies can access but small biotechs, rare disease sponsors, and academic developers cannot. Without addressing this, the NAM transition will widen the gap between large and small developers and concentrate approval power in big pharma.

Gap 6: The Legal Exposure Window

The guidance is a draft. Until it is finalized, it is legally vulnerable. Any sponsor whose IND is approved or rejected based on NAM data submitted under draft guidance could challenge the decision. More importantly, competing interests (animal testing contract research organizations, established pharmaceutical companies with sunk cost in animal study infrastructure) could challenge the guidance itself. The guidance currently lacks a fully developed evidentiary record that would defeat an 'arbitrary and capricious' challenge.

Gap 7: International Harmonization Gap

FDA cannot alone create global confidence in NAMs. European Medicines Agency (EMA) and Japan's PMDA still require traditional animal data for most applications. A U.S.-only NAM pathway creates a two-track system that adds cost and complexity for global drug developers. Without international harmonization, the practical uptake will be limited.

Gap 8: No Mandatory NAM-First Reporting Requirement

The current framework incentivizes NAM use but does not require sponsors to explain why they chose animals when a validated NAM alternative exists. There is no accountability mechanism — and therefore no ability to measure progress or identify where systemic change is happening vs. where legacy behavior is entrenched.

Gap 9: Pediatric, Rare Disease, and Diverse Population Gaps

Existing NAM platforms are largely calibrated on adult, non-diverse cell lines. Pediatric disease models, rare genetic disease models, and models incorporating biological sex differences are significantly underdeveloped. This limits the utility of NAMs for the populations who most need better drug safety data.

Gap 10: The Digital Twin and Physiological Digital Twin Infrastructure Gap

The most transformative long-term NAM technology — patient-specific digital twins that simulate entire pharmacokinetic/pharmacodynamic responses — requires a national data infrastructure that does not yet exist at the scale needed for regulatory use. Current pilot programs are promising but isolated.

SECTION III: 24 NEXT-GENERATION INNOVATIONS — WHAT IS NOT YET BEING DONE

Every proposal in this section: (1) builds on the existing framework without contradicting it; (2) can be implemented through existing agency authority under the FDA Modernization Act 2.0, the APA, and HHS organizational authority — no legislative changes required; and (3) is designed to be legally durable against challenge.

CLUSTER A: ACCELERATING VALIDATION (Solving Gap 1)

Innovation 1: The NAM Fast-Track Qualification Pathway (NAM-FTQ)

Modeled on the FDA's Breakthrough Therapy Designation for clinical drugs, create a formal 'NAM Fast-Track Qualification' program within CDER. When a NAM is submitted and generates favorable data in three or more independent IND/NDA applications, it automatically enters a Fast-Track Qualification review. CDER commits to a qualification decision within 180 days of Fast-Track entry.

- Basis: CDER already has the ISTAND program for Drug Development Tools — expand its scope and add the time commitment and staffing commitment.
- Legal basis: FDA Modernization Act 2.0; existing CDER DDT qualification authorities.
- Benefit: Converts the current ad hoc validation process into a systematic one. Creates market certainty for NAM developers and removes the 'perpetual pilot' problem.

> **PRECEDENT:** *Emulate's Human Liver-Chip was accepted into ISTAND's pilot program. The Fast-Track Qualification Pathway would be the full, permanent, time-bound version of that process — applied systematically across all organ systems.*

Innovation 2: Cross-Sponsor NAM Evidence Pooling (CSEP) Database

Require sponsors who submit NAM data in support of approved INDs to contribute de-identified, standardized NAM datasets to a federated FDA database. The CSEP database becomes the cumulative evidence base from which population-level NAM validation is built — without any individual sponsor bearing the full cost of validation.

- Basis: FDA already has authority under 21 CFR 312 to condition IND processes. The NIH NAMs Data Hub and Coordinating Center (NDHCC) funded by Complement-ARIE is the natural home for this infrastructure.
- Legal basis: FDA can require data submission as a condition of IND authorization; existing data-sharing frameworks under 21st Century Cures Act.
- Benefit: Solves the interoperability problem. Within three years, produces the largest NAM evidence base in the world — in the U.S. government's hands.

CLUSTER B: REVIEWER CAPACITY AND TRAINING (Solving Gap 3)

Innovation 3: NAM Specialist Reviewer Cadre

Establish a dedicated NAM Specialist Reviewer cadre within CDER, CBER, and CDRH — reviewers with advanced training in microphysiological systems, computational toxicology, and AI-driven ADMET modeling. Pair every sponsor submitting a novel NAM package with a NAM Specialist Reviewer as the primary reviewer rather than a traditional pharmacologist.

- Basis: CDER already uses specialty reviewers for complex biologics and gene therapies. This extends that model to NAMs.
- Resource plan: Start with 20-30 NAM specialists across CDER/CBER, recruited from industry, academia, and NIH ORIVA. Scale to 100 within three years.
- Companion action: Partner with NIH ORIVA and the Complement-ARIE TDCs to run a quarterly NAM Reviewer Training Exchange — FDA reviewers visit NIH tissue chip labs; NIH scientists spend time in FDA review divisions.

Innovation 4: FDA NAMs Academy — Public Reviewer Training Program

Create a free, online FDA NAMs Academy — a structured certification program for FDA reviewers, industry scientists, and academic researchers covering the science, regulatory framework, and data evaluation standards for every major NAM category. Publish all course materials as open-access.

- Benefit: Builds the national scientific literacy needed for broad NAM adoption. Creates a common vocabulary between sponsors and reviewers. Eliminates the information asymmetry that currently delays NAM submissions.
- Precedent: FDA already runs the FDA Science and Research Special Topics program and the FDA-TRACK initiative. This is a natural extension.

CLUSTER C: STANDARDS AND DATA INFRASTRUCTURE (Solving Gaps 4 and 10)

Innovation 5: The FAIR-NAM Data Standards Initiative

Convene a public-private working group — FDA, NIH, USP, NIST, and the pharmaceutical industry (through the IQ Consortium's Microphysiological Systems Affiliate) — to develop and publish Findable, Accessible, Interoperable, and Reusable (FAIR) data standards for every major NAM category within 24 months. Mandate FAIR compliance for all NAM data submitted in FDA applications.

- Basis: NIST has existing authority over standards development; FDA has authority over submission requirements.
- Benefit: Makes NAM datasets comparable across sponsors, platforms, and organ systems. Unlocks the cross-sponsor pooling described in Innovation 2. Positions the U.S. as the global standard-setter, increasing pressure on EMA and PMDA to align.

Innovation 6: The National Digital Twin Infrastructure Program

Direct NIH and NSF (in partnership with ARPA-H) to fund a National Digital Twin Infrastructure Program — a cloud-based, privacy-protected platform that aggregates de-identified real-world health data, genomic data, and EHR data to train population-level computational pharmacokinetic/pharmacodynamic (PK/PD) models. These models become the foundation for digital twin NAM submissions.

- Current state: Complement-ARIE pilot projects include patient avatars for gynecological diseases and computational GI models. These are proof-of-concept. This Innovation scales them to a national platform.
- Precedent: The UK Biobank and Estonia's national digital twin initiative demonstrate feasibility. The U.S. has the NIH All of Us Research Program as the data foundation.
- Legal basis: ARPA-H Act (2022); HHS Secretary authority over NIH program priorities; existing NIH All of Us data infrastructure.
- Benefit: Within five years, sponsors will be able to run drug candidates through a computational population model representing 500,000+ diverse Americans before ever entering an IND — dramatically reducing both animal studies and Phase I failures.

CLUSTER D: LEGAL HARDENING — PROTECTING THE GUIDANCE FROM CHALLENGE (Solving Gap 6)

Innovation 7: Pre-Emptive Evidentiary Record Building

The March 18 guidance was released as a draft with an open comment period. Before it is finalized, HHS and FDA must build an evidentiary record that would defeat an 'arbitrary and capricious' challenge under 5 U.S.C. Section 706. The three specific actions required:

- Commission and formally submit to the docket a systematic review of NAM predictivity vs. animal model predictivity, benchmarked against clinical outcomes, covering at least the six highest-volume drug toxicity categories (hepatotoxicity, cardiotoxicity, nephrotoxicity, neurotoxicity, reproductive toxicity, carcinogenicity).
- Formally address the WPATH-equivalent scientific opposition: the primary industry counter-argument is that premature NAM adoption creates AI-bias risks in study design. The final guidance preamble must specifically address and rebut this argument with evidentiary support.
- Incorporate DOJ SafetAI Initiative findings: FDA's own SafetAI program has developed deep-learning QSAR models for hepatotoxicity, carcinogenicity, mutagenicity, nephrotoxicity, and cardiotoxicity. Formally incorporate SafetAI validation data into the final guidance's administrative record.

> **LEGAL PRIORITY:** *Courts reviewing final agency guidance apply an 'arbitrary and capricious' standard. A guidance that is well-reasoned, addresses significant scientific objections, and is grounded in a robust evidentiary record will survive challenge. One that is not will not. This is the most important single action on this list.*

Innovation 8: The NAM Safe Harbor Rule

Promulgate a formal NAM Safe Harbor Rule: any sponsor who submits a drug application supported by NAM data that meets the four core validation principles in the March 18 guidance cannot have that application rejected on the basis of insufficient nonclinical data without specific written findings from FDA detailing what additional data is required and why the NAM data was insufficient. This creates due process for sponsors and a documented record for FDA.

- Legal basis: FDA Modernization Act 2.0; APA notice-and-comment rulemaking.
- Benefit: Removes the chilling effect that currently prevents sponsors from submitting NAM data out of fear of rejection without explanation. Creates accountability and a documentation trail that strengthens, not weakens, the guidance against legal challenge.

Innovation 9: The 'NAM-First' Documentation Requirement

Amend IND application instructions (21 CFR 312) to require sponsors to include a brief 'NAM Consideration Statement' when they elect to use animal models instead of an available validated NAM for any nonclinical study. The statement would document which NAMs were considered and why they were not selected.

- This is not a restriction — sponsors retain full freedom to use animals. It is a documentation requirement.
- Legal basis: FDA authority under 21 CFR 312; FDA Modernization Act 2.0.
- Benefit: Creates the measurement infrastructure needed to track progress toward the 3-5 year animal reduction goal. Without data on where animals are still being used and why, there is no way to target subsequent guidance efforts. Also creates a self-generating database of NAM adoption barriers.

CLUSTER E: EXPANDING ACCESS — SMALL SPONSORS AND RARE DISEASES (Solving Gap 5)

Innovation 10: The NAM Access Grant Program

Create a dedicated NAM Access Grant Program — funded through NIH and administered jointly with FDA — that provides direct financial support and infrastructure access to small biotechs, rare disease sponsors, academic research groups, and minority-owned pharmaceutical developers to conduct NAM-based nonclinical studies.

- Funding model: $50M annually, structured as a matching grant (sponsor contributes 25%, grant covers 75%) for NAM study costs.
- Infrastructure component: Negotiate consortium agreements with Wyss Institute, Emulate, Organovo, and other major NAM platform providers to make their systems available at subsidized rates to grant recipients.
- Legal basis: NIH grant authority; SBIR/STTR program frameworks.
- Benefit: Prevents the NAM transition from becoming a tool of incumbent pharmaceutical dominance. Levels the playing field for rare disease innovators who currently cannot afford traditional animal testing programs.

Innovation 11: The NAM Consulting Desk

Establish a dedicated 'NAM Consulting Desk' within CDER — a rapid-response team of NAM specialists available to answer sponsor questions about NAM suitability, study design, and data submission requirements within 10 business days, free of charge. This is distinct from the formal pre-IND meeting process.

- Modeled on the FDA's existing Rare Pediatric Disease Designation process, which includes informal consultation.
- Benefit: Removes the information barrier that currently discourages smaller sponsors from attempting NAM submissions. Makes the guidance actionable for everyone, not just companies with large regulatory affairs departments.

CLUSTER F: DIVERSITY, PEDIATRICS, AND RARE DISEASE NAMs (Solving Gap 9)

Innovation 12: The Pediatric and Diverse Population NAM Initiative

Direct the Complement-ARIE Technology Development Centers to explicitly prioritize development of NAM platforms incorporating: (1) pediatric-age cell biology and developmental pharmacology; (2) biological sex differences in drug metabolism; (3) ancestrally diverse cell lines representing African, Asian, Indigenous, and Hispanic genetic backgrounds.

- Current gap: Virtually all existing validated NAMs use adult, predominantly European-ancestral cell lines. This creates the same systematic bias that has historically made clinical trials unrepresentative — only replicated in vitro.
- Complement: The NIH All of Us Research Program has collected genomic and health data from 750,000+ participants representing diverse populations. Partner Complement-ARIE TDCs directly with All of Us to source diverse iPSC lines for NAM development.
- Legal basis: Complement-ARIE program authority; NIH grant conditions.

Innovation 13: Rare Disease NAM Exemption Framework

For drugs targeting ultra-rare diseases (fewer than 1,000 patients in the U.S.), create a Rare Disease NAM Exemption that permits full IND/NDA submission supported exclusively by NAM data, with no animal study requirement, provided the sponsor demonstrates: (1) no validated animal model exists for the target disease; (2) the NAM used is human-cell-based; and (3) the sponsor provides a patient-level compassionate use monitoring protocol.

- Basis: FDA already grants substantial flexibility in rare disease drug development under the Orphan Drug Act. This formalizes the NAM pathway within that framework.
- Benefit: The populations who most need faster cures — rare disease patients — would be first to benefit from the full power of human-relevant models.

CLUSTER G: INTERNATIONAL HARMONIZATION (Solving Gap 7)

Innovation 14: The ICH NAM Working Group

Direct FDA's international affairs office to formally propose establishment of a new ICH (International Council for Harmonisation) Working Group specifically dedicated to NAM validation standards and regulatory acceptance criteria. Target a joint FDA-EMA-PMDA NAM harmonization guidance within 36 months.

- Precedent: ICH already has working groups on computational pharmacology (M15) and bioanalytical method validation (M10). An NAM-specific group is the natural next step.
- Benefit: A drug approved in the U.S. on NAM data that is not accepted by EMA creates a split regulatory world that adds cost and reduces uptake. Harmonization multiplies the value of every U.S. NAM investment.

Innovation 15: Bilateral NAM Recognition Agreements

While the ICH process proceeds (which takes years), pursue bilateral NAM data-sharing and mutual recognition agreements with EMA, Health Canada, MHRA (UK), TGA (Australia), and Japan's PMDA. Under these agreements, NAM data accepted by one agency in a drug application would be recognized by partner agencies without re-review.

- Legal basis: FDA Commissioner authority under existing MOU frameworks with international counterparts; no new legislation required.
- Benefit: Immediately reduces the cost of global drug development using NAMs, creating a powerful market incentive for sponsor adoption.

CLUSTER H: AI AND NEXT-GENERATION COMPUTING (Next-Generation Technologies)

Innovation 16: The FDA SafetAI Platform — Public Release

FDA's internal SafetAI Initiative has developed deep-learning QSAR models for five critical toxicity endpoints: hepatotoxicity, carcinogenicity, mutagenicity, nephrotoxicity, and cardiotoxicity. These models — trained on the world's largest proprietary toxicology dataset — should be released as open-access tools available to all drug developers.

- Current state: SafetAI models are internal FDA tools. They are not publicly accessible.
- Proposed action: Release SafetAI models through an open API that sponsors can use to pre-screen drug candidates before IND submission. Results can be included in IND applications as supporting computational NAM data.
- Legal basis: FDA Commissioner authority over FDA regulatory science tools; open government data policies.
- Benefit: Every drug developer in the country gains access to FDA's best AI toxicology models — for free. Dramatically reduces the computational barrier to NAM adoption. Also creates a feedback loop: when sponsors submit their own NAM data, the SafetAI models can be updated, creating a continuously improving public resource.

Innovation 17: Federated Learning NAM Network

Implement a federated learning framework — where multiple pharmaceutical companies, academic labs, and hospitals train a shared AI toxicology model on their local datasets without sharing the underlying data — to build the world's most predictive cross-institutional drug safety model. The MELLODDY project in Europe demonstrated this works for QSAR models; apply it specifically to NAM datasets.

- Basis: NIH Common Fund has existing authority to fund federated research infrastructure; FDA can participate as a data node.
- Benefit: Solves the data scarcity problem that limits AI model training without requiring any company to share proprietary data. Creates a public-private model that is legally and competitively clean.

Innovation 18: AI-Powered NAM Protocol Optimizer

Fund development of an AI tool that takes a drug candidate's molecular structure as input and recommends the optimal NAM protocol for that specific compound's toxicity profile — suggesting which organ-on-chip platforms to use, which computational models to run, and in what sequence, to generate the most comprehensive safety package at lowest cost and time.

- This is analogous to AI-powered clinical trial design tools that are already transforming Phase II/III trial efficiency.
- Benefit: Democratizes expert NAM study design. A small biotech with no NAM experience can generate an optimal study design in hours rather than months.

CLUSTER I: ACCELERATING THE ENDGAME — PHASING OUT SPECIFIC ANIMAL MODELS

Innovation 19: The Rat LD50 Phase-Out Timeline

The rat acute oral toxicity (LD50) test — which kills hundreds of thousands of animals annually in the U.S. — has validated computational replacements. QSAR models trained on ICE Rat Acute Toxicity data have demonstrated superior predictive performance for Globally Harmonized System (GHS) toxicity categories. Publish a formal 24-month phase-out timeline for the rat LD50 test, mandating transition to validated QSAR alternatives.

- Legal basis: FDA Modernization Act 2.0; CDER and CDRH existing regulatory authority. No Congressional action required.
- Precedent: The EU banned the rat LD50 test in 2009. The validated computational alternatives have been in existence for over a decade.

Innovation 20: The Rabbit Pyrogen Test (RPT) Final Phase-Out

The March 18 guidance on recombinant reagents for endotoxin testing begins this process. Complete it: publish a definitive phase-out timeline for the Rabbit Pyrogen Test (RPT), which kills an estimated 200,000 rabbits annually in the U.S. pharmaceutical industry. rFC and human monocyte activation tests (MAT) have been validated as superior alternatives.

- USP Chapter 86 (May 2025) already provides the pharmacopeial foundation. FDA needs only to publish the regulatory timeline.
- This is the single most impactful near-term animal reduction action available that requires no new science — only regulatory will.

Innovation 21: The Draize Rabbit Eye Test Replacement Protocol

For drug products tested for ocular toxicity using the Draize rabbit eye test, publish a replacement protocol based on the OECD-validated Reconstructed Human Cornea-like Epithelium (RhCE) test method. This method has been validated by EURL ECVAM and accepted by OECD. FDA recognition is the missing step.

CLUSTER J: TRANSPARENCY, ACCOUNTABILITY, AND INCENTIVES

Innovation 22: The Annual NAM Progress Report

Mandate an Annual NAM Progress Report — published by HHS and co-signed by FDA Commissioner and NIH Director — that tracks, by drug category and organ system: (1) total NAM submissions received; (2) total animal studies replaced or reduced; (3) number of validated NAMs; (4) drug approval timelines for NAM-supported vs. animal-supported INDs.

- Without measurement, there is no accountability. Without accountability, there is no pressure on entrenched interests.
- Legal basis: HHS Secretary reporting authority; existing FDA transparency mandates.

Innovation 23: The NAM Innovation Prize

Establish an annual HHS-sponsored NAM Innovation Prize — $5M award for the NAM that demonstrated the most statistically significant improvement in human clinical predictivity over the prior animal model in its category during the preceding year. Partner with the Foundation for the NIH to fund the prize.

- Precedent: DARPA Challenge prizes have catalyzed breakthrough technologies in AI, autonomous vehicles, and biosecurity. A well-structured prize creates innovation incentives that no grant can replicate.
- Bipartisan appeal: This initiative has natural bipartisan support — animal welfare advocates and fiscal conservatives both support eliminating expensive, inefficient animal testing. A prize competition generates positive media and public engagement.

Innovation 24: The NAM Regulatory Sandbox

Establish a formal 'NAM Regulatory Sandbox' — a pre-competitive space where drug developers can test novel NAM approaches with FDA in real-time, without the results affecting their IND status, in exchange for contributing the data to the public CSEP database described in Innovation 2.

- Modeled on the FCA (UK Financial Conduct Authority) regulatory sandbox, which allowed fintech innovators to test new financial products with regulatory oversight before full market launch.
- Benefit: Dramatically accelerates the development of NAMs that are not yet ready for primary IND use but are promising enough to generate valuable data. Removes the binary 'validated or not' barrier. Creates a safe space for scientific risk-taking.

SECTION IV: COMPLETE RESOURCE AND DOCUMENTATION LIBRARY

The following resources are organized into seven categories. Every resource listed is active, publicly accessible, and directly actionable in support of the proposals in this memo.

A. Controlling Statutes and Executive Authority

#	Resource
1	**FDA Modernization Act 2.0 (P.L. 117-328, Dec. 2022)** *congress.gov/bill/117th-congress/house-bill/7667* Removes the statutory animal testing requirement for new drugs. Explicitly permits organoids, organ-on-chip, microphysiological systems, and computational models as primary evidence in drug applications. ***USE: Cite in all final guidance preambles as the controlling statutory authority. Reference in every NAM submission to establish Congressional mandate.***
2	**FDA Modernization Act 3.0 (Introduced April 11, 2025 — H.R. pending)** *akingump.com/en/insights/blogs/eye-on-fda/ (see April 2025 entry)* Would require full implementation of FDA Modernization Act 2.0 and direct FDA to implement provisions reducing unnecessary animal testing. ***USE: Monitor Senate trajectory. Support passage as the legislative complement to existing administrative authority.***
3	**Executive Order 14187: Protecting Children from Chemical and Surgical Mutilation (Jan. 2025)** *federalregister.gov — search EO 14187* While primarily targeting gender procedures, Section 5 directs HHS to use all available authority to protect children from unnecessary medical interventions — the same authority basis supports mandatory review of animal-derived pediatric pharmacology data. ***USE: Cite as additional Executive authority for pediatric NAM Initiative (Innovation 12).***
4	**MAHA Commission Strategy Report** *Available via HHS.gov* Explicitly recommends reducing reliance on animal studies that often fail to replicate complex human conditions. Provides Executive Branch political authorization for the entire NAM initiative. ***USE: Cite in final guidance preamble as policy basis.***

B. Active FDA Regulatory Documents (Comment & Implementation)

#	Resource
5	**ACTIVE COMMENT: Draft Guidance on NAMs in Drug Development — FDA-2025-D-6131** *regulations.gov — Docket: FDA-2025-D-6131 | Comments due: May 18, 2026*

	The foundational draft guidance. Four core validation principles. Explicitly states validation is not required for NAM submissions. ***USE: Submit formal comments by May 18, 2026 supporting the innovations in this memo. Comments from HHS leadership and interagency partners strengthen the administrative record.***
6	**FDA Roadmap to Reducing Animal Testing in Preclinical Safety Studies (April 2025)** *fda.gov/files/newsroom/published/roadmap_to_reducing_animal_testing_in_preclinical_safety_studies.pdf* 3-5 year strategic plan. Covers mAbs, small molecules, biologics. Identifies specific NAM categories and their current validation status. ***USE: Foundation document for all subsequent actions. Cross-reference in all proposed rules and guidance.***
7	**FDA Draft Guidance: Reducing NHP Testing for Monoclonal Antibodies (December 2025)** *fda.gov/regulatory-information/search-fda-guidance-documents* Product-specific NAM pathway for the single highest-demand animal testing category. ***USE: Model for subsequent product-specific NAM guidance documents (small molecules, oncology biologics, gene therapies).***
8	**FDA Guidance: Pyrogen and Endotoxins Testing — Level 2 Revision (March 18, 2026)** *fda.gov — search: Pyrogen Endotoxins Testing Questions and Answers* Enables transition from horseshoe crab-derived LAL to recombinant rFC for endotoxin testing. ***USE: Cite as precedent for Innovation 20 (Rabbit Pyrogen Test phase-out).***
9	**FDA ISTAND Program — Innovative Science and Technology Approaches for New Drugs** *fda.gov/news-events/fda-voices/fda-advances-drug-development-innovation-establishing-istand-permanent-qualification-program* The permanent DDT qualification program into which the Liver-Chip was accepted. Template for Innovation 1 (NAM-FTQ). ***USE: Model the NAM Fast-Track Qualification pathway on ISTAND's framework. Expand ISTAND's scope explicitly to include organ-on-chip, organoid, and AI-NAM categories.***
10	**FDA SafetAI Initiative** *fda.gov/about-fda/nctr-research-focus-areas/safetai-initiative* FDA/CDER/NCTR deep-learning QSAR models for five toxicity endpoints. Currently internal only. ***USE: Basis for Innovation 16 (SafetAI Public Release). This is ready technology sitting on a shelf.***

C. NIH Programs and Funding Infrastructure

#	Resource
11	**NIH Complement-ARIE Program ($150M, March 18, 2026)** *commonfund.nih.gov/complementarie	nih.gov/news-events/news-releases/nih-invests-150-million-human-based-research-reduce-use-animal-models* First awards announced March 18, 2026. Establishes Technology Development Centers, NAMs Data Hub, Validation and Qualification Network. $7M NAMs Reduction to Practice Challenge.

	USE: Home for Innovation 2 (CSEP Database), Innovation 5 (FAIR-NAM Standards), and Innovation 12 (Pediatric/Diverse Population NAMs).
12	**NIH ORIVA — Office of Research Innovation, Validation, and Application (est. April 29, 2025)** *Available via NIH.gov* NIH's interagency coordination hub for NAM development, validation, and regulatory translation. ***USE: Partner ORIVA with Innovation 3 (NAM Specialist Reviewer Cadre) training exchange program.***
13	**NIH $87M Organoid Development Center** *Available via NIH.gov* Dedicated center for organoid standardization and validation. ***USE: Natural home for Innovation 12 (Pediatric/Diverse Cell Line Initiative).***
14	**Johns Hopkins DROIDp Platform ($15M NIH Complement-ARIE Award)** *publichealth.jhu.edu/2026/johns-hopkins-researchers-awarded-15-million* Brain organoid + AI analytics platform for neurological drug testing. Uses human stem cell-derived neural tissues with advanced electrical sensors. ***USE: Showcase as the model for future TDC awards; expand to Alzheimer's, SYNGAP1, and pediatric neurology applications.***
15	**NIH All of Us Research Program** *allofus.nih.gov* 750,000+ participant genomic and health dataset representing unprecedented population diversity. ***USE: Foundation for Innovation 6 (National Digital Twin Infrastructure) and Innovation 12 (Diverse Cell Line sourcing).***

D. International Precedents and Scientific Validation Resources

#	Resource
16	**EU REACH Regulation — OECD Test Guideline 431/439 (RhCE for Ocular/Skin Toxicity)** *oecd.org/chemicalsafety/testing/oecdguidelinesforthetestingofchemicals.htm* OECD-validated Reconstructed Human Cornea-like Epithelium test methods, accepted globally. Ready for FDA adoption. ***USE: Basis for Innovation 21 (Draize rabbit eye test replacement).***
17	**ICH M15: Model-Informed Drug Development (MIDD) Guideline** *ich.org/page/multidisciplinary-guidelines* Existing ICH framework for computational pharmacology in drug development. Template for proposed ICH NAM Working Group (Innovation 14). ***USE: Use M15 as the structural model for the proposed ICH NAM harmonization guideline.***
18	**MELLODDY Federated Learning Project (EU Horizon 2020)** *melloddy.eu*

	Demonstrated that 10 pharmaceutical companies could train shared QSAR models via federated learning without sharing proprietary data. Achieved superior predictive performance vs. local models. ***USE: Basis for Innovation 17 (Federated Learning NAM Network). This is proven technology.***
19	**Emulate Human Liver-Chip — ISTAND Pilot Acceptance** *fda.gov/drugs/drug-safety-and-availability/fdas-istand-pilot-program-accepts-submission-first-organ-chip-technology* First organ-on-chip accepted into FDA's regulatory qualification program. Outperformed rat liver models for DILI prediction across 27 drugs. ***USE: Showcase as the proof of concept for all subsequent organ-chip qualification. Use DILI outperformance data in the anti-arbitrary-and-capricious record.***
20	**Harvard Wyss Institute Organ Chip Research (Dr. Donald Ingber)** *Cell Stem Cell, 2026 Feb 5;33(2):176-183	wyss.harvard.edu* Peer-reviewed analysis of organ chip challenges and opportunities in FDA assessments. Published January 2026. ***USE: Commission expert declaration from Ingber lab for the final guidance administrative record.***
21	**OECD QSAR Toolbox and OECD 5 Principles for Model Validation** *qsartoolbox.org	oecd.org* The internationally accepted framework for QSAR model validation in regulatory contexts. ***USE: Basis for Innovation 5 (FAIR-NAM Data Standards). OECD principles provide the international foundation.***
22	**IQ Consortium Microphysiological Systems Affiliate** *iqconsortium.org* Public-private partnership of pharmaceutical industry partners developing MPS/organ-chip standards. ***USE: Key industry partner for Innovation 2 (CSEP Database), Innovation 5 (FAIR-NAM Standards), and Innovation 7 (Evidentiary Record).***

E. Key Peer-Reviewed Scientific Literature for Administrative Record

#	Resource
23	**Ingber et al., 'Challenges and Opportunities for Human Organ Chips in FDA Assessments and Pharma Pipelines,' Cell Stem Cell (2026)** *cell.com/cell-stem-cell/abstract/S1934-5909(25)00456-4	PubMed: 41564882* Peer-reviewed analysis showing organ chips' current FDA assessment relevance and pipeline integration challenges. Authored by the Wyss Institute founder. ***USE: Include in final guidance docket as primary scientific support for organ-on-chip NAM category.***
24	**MDPI, 'Organs-on-Chips in Drug Development: Engineering Foundations, AI, and Clinical Translation' (2026)** *mdpi.com/2079-6374/16/3/155* Benchmarking: cardiac OoCs achieving AUROC >= 0.85 for torsadogenic risk; renal chips outperforming conventional in vitro assays for transporter-mediated clearance.

	USE: Quantitative benchmarking data for the administrative record — precisely the kind of evidence needed to defeat an arbitrary and capricious challenge.
25	**Frontiers in Chemistry: 'Recent Advances in AI-Based Toxicity Prediction for Drug Discovery' (2025)** *frontiersin.org/journals/chemistry/articles/10.3389/fchem.2025.1632046/full* Comprehensive review of AI toxicity prediction advances including federated learning (MELLODDY), QSAR models, and regulatory acceptance under ICH M7(R2) and S1B(R1). ***USE: Scientific foundation for Innovation 16 (SafetAI Public Release) and Innovation 17 (Federated Learning Network).***
26	**NIH/Oxford: 'Complement-ARIE: Catalyzing the Development and Adoption of New Approach Methodologies,' ScienceDirect (2025)** *sciencedirect.com/science/article/pii/S3050620425000211* NIH's own peer-reviewed description of the Complement-ARIE program's goals, evidence base, and scientific opportunities. ***USE: Include in final guidance docket as formal NIH interagency scientific support.***
27	**Wiley Advanced Science: 'Machine Learning-Enabled Drug-Induced Toxicity Prediction' (Feb 2025)** *advanced.onlinelibrary.wiley.com/doi/10.1002/advs.202413405* Unexpected toxicity accounts for 30% of drug development failures. ML innovations in DILI, cardiotoxicity, and neurotoxicity prediction. ***USE: Key statistic — 30% of drug failures caused by toxicity not predicted by animal models — for the guidance preamble's case for NAM adoption.***

SECTION V: CONSOLIDATED PRIORITY ACTION CHECKLIST

Organized by timeline. All actions are within existing HHS/FDA/NIH authority. No legislative changes required.

IMMEDIATE (0-30 Days)

☐	Submit formal HHS/FDA interagency comment to FDA-2025-D-6131 docket before May 18, 2026 incorporating Innovations 7, 8, and 9 (legal hardening package)	**Innovation 7, 8, 9**
☐	Commission the systematic NAM vs. animal predictivity review needed for the final guidance evidentiary record	**Innovation 7**
☐	Direct FDA to publicly release SafetAI models via open API — internal validation already complete	**Innovation 16**
☐	Establish NAM Consulting Desk within CDER — can be done by internal reorganization with no new authority needed	**Innovation 11**

SHORT-TERM (30-180 Days — Before Final Guidance)

- Finalize NAM Fast-Track Qualification Pathway design within ISTAND framework (Innovation 1)
- Launch FAIR-NAM Data Standards working group with IQ Consortium, NIST, and USP (Innovation 5)
- Direct Complement-ARIE TDCs to formally include pediatric and diverse cell line requirements in grant terms (Innovation 12)
- Begin development of NAM Specialist Reviewer Cadre — post positions, begin recruitment from NIH ORIVA and academic partners (Innovation 3)
- Publish rat LD50 phase-out timeline — validated replacements already exist (Innovation 19)
- Publish Rabbit Pyrogen Test phase-out timeline — USP Chapter 86 provides the pharmacopeial foundation (Innovation 20)
- Propose ICH NAM Working Group through FDA's international affairs office (Innovation 14)

MEDIUM-TERM (180 Days - 2 Years)

- Finalize the March 18 NAMs guidance with robust evidentiary record incorporating Innovations 7-9
- Promulgate NAM Safe Harbor Rule via formal notice-and-comment rulemaking (Innovation 8)
- Launch NAMs Academy as open-access online training platform (Innovation 4)
- Execute bilateral NAM recognition agreements with EMA, Health Canada, MHRA (Innovation 15)

- Publish Rare Disease NAM Exemption Framework guidance (Innovation 13)
- Fund National Digital Twin Infrastructure Program through ARPA-H (Innovation 6)
- Launch NAM Access Grant Program — $50M annually — for small sponsors and rare disease developers (Innovation 10)
- Launch NAM Innovation Prize with Foundation for the NIH (Innovation 23)

DURABLE (2-5 Years)

- Publish first Annual NAM Progress Report (Innovation 22)
- Achieve ICH NAM Harmonization Guideline (Innovation 14)
- Establish National Digital Twin platform with 500,000+ participant data foundation (Innovation 6)
- Publish Draize rabbit eye test FDA replacement protocol (Innovation 21)
- Scale Federated Learning NAM Network to 25+ institutional participants (Innovation 17)
- Complete full deployment of NAM Regulatory Sandbox (Innovation 24)
- Achieve full post-quantum secure blockchain integration across NAMs Data Hub, CSEP Database, and FDA submission infrastructure (PQC Innovations 25-30)

SECTION VI: POST-QUANTUM SECURE BLOCKCHAIN INFRASTRUCTURE

Every NAM data system in this memo generates, transmits, and stores scientific data whose integrity must be beyond reproach. A single data tampering event could invalidate an entire category of NAM evidence and set back the initiative by years. This section integrates Post-Quantum Cryptographic (PQC) secured blockchain technology across the NAMs infrastructure.

THE QUANTUM THREAT IS NOW: *In August 2024, NIST finalized its first three post-quantum cryptographic standards (FIPS 203, 204, 205). Under NIST IR 8547, all U.S. federal systems must deprecate quantum-vulnerable cryptographic algorithms by 2035. Building the NAMs infrastructure on PQC-secured blockchain from Day 1 is not just prudent — it is the federally mandated direction of travel.*

LEGAL AND REGULATORY FOUNDATION

Legal Authority	Application to NAMs Infrastructure
21 CFR Part 11	Requires immutable, time-stamped audit trails for all FDA-regulated electronic records. A PQC-secured permissioned blockchain satisfies and exceeds this standard — providing tamper-proof data provenance that is mathematically impossible to alter.
NIST FIPS 203/204/205 + IR 8547	August 2024 finalized PQC standards approved for immediate federal use. IR 8547 mandates migration by 2035, with high-risk systems earlier. NAMs data is high-risk: it underlies drug approval decisions affecting millions of Americans.
Quantum Cybersecurity Preparedness Act + EO 14144	Requires federal agencies to prepare PQC migration plans. All new FDA-funded data infrastructure built in 2026 and beyond must be PQC-compliant from inception — not retrofitted at 10x the cost.
FDA Modernization Act 2.0	Permits NAM data as primary evidence in drug applications. The integrity of that data must be verifiable by FDA reviewers at any time. Blockchain provides the cryptographic proof of data lineage that makes NAM submissions litigation-proof.

ARCHITECTURE NOTE: *All six innovations below use a permissioned blockchain (Hyperledger Fabric or equivalent) — NOT a public cryptocurrency blockchain. Permissioned blockchains are high-speed, HIPAA-compatible, and interoperable with existing FDA infrastructure. Only a cryptographic hash (digital fingerprint) of the data is stored on-chain — the data itself remains in existing secure systems, preserving proprietary confidentiality.*

INNOVATIONS 25-30: PQC BLOCKCHAIN APPLICATIONS

Innovation 25: PQC-Secured NAMs Data Hub — The Trust Layer

Integrate PQC-secured blockchain as the trust layer for the NIH Complement-ARIE NAMs Data Hub. Every NAM dataset — organ-on-chip results, organoid data, AI-generated ADMET predictions — receives a NIST FIPS 204 (ML-DSA) cryptographic hash anchored to the permissioned blockchain at the moment of submission.

- FDA reviewer benefit: Verify in seconds that any NAM data package has not been modified since generation. Cryptographic proof of integrity — not just a compliance checkbox.
- Legal benefit: Eliminates the data manipulation attack vector that opposing counsel will use to challenge NAM-supported drug approvals. The blockchain provides irrefutable mathematical proof.
- Precedent: The Scrybe system (PMC10629820) demonstrated this exact architecture using Hyperledger Fabric with 100% tamper detection and negligible performance overhead.

Innovation 26: PQC-Secured Cross-Sponsor Evidence Pooling (CSEP) Ledger

The CSEP database (Innovation 2) must use PQC-secured blockchain to establish irrefutable data provenance for every contributed NAM dataset. Smart contracts automate credential verification, timestamping, regulatory context recording, and permanent chain-of-custody documentation. No human — not even FDA administrators — can alter this record.

- Multi-Party Verification: Any party — FDA, sponsor, auditor, or court — can independently verify dataset authenticity and integrity.
- HIPAA/Trade Secret Compliance: Only cryptographic hashes stored on-chain. Validated in the Japanese Cabinet Office regulatory sandbox (PMC7298640).

Innovation 27: Quantum-Resistant Digital Signatures for All NAM FDA Submissions

Amend FDA eCTD submission requirements to accept and ultimately require NIST FIPS 204 (ML-DSA) post-quantum digital signatures on all NAM data packages in INDs, NDAs, and BLAs. Current eCTD submissions use RSA and ECDSA — both quantum-vulnerable and scheduled for deprecation by 2030 under NIST IR 8547.

- Transition: (1) 2026: Accept ML-DSA as optional. (2) 2027: Require ML-DSA for NAM data. (3) 2030: Require ML-DSA for all eCTD submissions.
- Benefit: Any drug approved on NAM data signed with ML-DSA will have its evidentiary record protected in perpetuity — even after quantum computers can break RSA.

Innovation 28: Blockchain-Anchored NAM Validation Registry

A publicly accessible, blockchain-anchored NAM Validation Registry — a tamper-proof real-time record of every NAM submitted, qualified, or validated through FDA ISTAND and the NAM Fast-Track Qualification Pathway. Every validation event is an immutable blockchain transaction. No one can retroactively modify a NAM qualification history.

- Eliminates information asymmetry: any sponsor, researcher, or regulator queries the registry in real time rather than re-contacting FDA for status.
- Prevents qualification inflation: because records are blockchain-anchored, a NAM status cannot expand beyond what was actually validated.

Innovation 29: PQC-Secured Federated Learning Integrity Protocol

The Federated Learning NAM Network (Innovation 17) is vulnerable to model poisoning attacks — where a malicious participant submits corrupted model updates that cause the shared AI toxicology model to generate dangerously incorrect predictions. Apply NIST FIPS 205 (SLH-DSA) post-quantum hash-based signatures to every model update, making model poisoning attacks mathematically infeasible.

- Identified risk: The MELLODDY project explicitly flagged model poisoning as the primary security threat in pharmaceutical federated learning. PQC signatures are the solution.

Innovation 30: National Digital Twin Identity Infrastructure — PQC Sovereign Identity

Each participant in the National Digital Twin program receives a PQC Decentralized Identifier (DID) anchored to the permissioned blockchain using ML-KEM (NIST FIPS 203). Data contributions link to DIDs — not to personally identifiable information. Smart contracts encode and enforce consent permissions, with revocations automatically propagated and immutably recorded.

- Trust foundation: If participants cannot trust their data is secure against future quantum attacks, participation declines. PQC-secured sovereign identity is the foundation of the Digital Twin program trust model.
- Alignment: Fully compatible with NIH All of Us Research Program governance and the 21st Century Cures Act interoperability requirements.

PQC BLOCKCHAIN IMPLEMENTATION TIMELINE

Phase	Action	Innovation
IMMEDIATE (0-60 days)	Direct NIH NDHCC to build Complement-ARIE NAMs Data Hub on Hyperledger Fabric with NIST FIPS 204 ML-DSA signing from Day 1. Build it in — do not retrofit.	**Innovation 25**
SHORT-TERM (60-180 days)	Launch blockchain-anchored NAM Validation Registry; accept ML-DSA as optional eCTD signature; issue CSEP smart contract architecture specifications.	**Innovations 26, 27, 28**
MEDIUM-TERM (180 days-2 yrs)	Deploy PQC signature integrity protocol for Federated Learning Network; implement PQC DID sovereign identity for Digital Twin participants.	**Innovations 29, 30**
DURABLE (2027-2030)	Require ML-DSA for all NAM eCTD submissions (2027). Full PQC migration of FDA submission	**Innovation 27 (full)**

	infrastructure (2030). Achieve the first fully quantum-resistant drug approval record in history.	

PQC BLOCKCHAIN SUPPORTING RESOURCES

#	Resource
28	**NIST FIPS 203/204/205 — PQC Standards (August 2024)** *csrc.nist.gov/projects/post-quantum-cryptography | nist.gov/pqc* Three finalized federal PQC standards: ML-KEM (key encapsulation), ML-DSA (digital signatures), SLH-DSA (hash-based signatures). Approved for immediate federal use August 14, 2024. ***USE: Mandatory compliance standards for all Innovation 25-30 implementations. Cite in all NAMs data infrastructure procurement specifications.***
29	**NIST IR 8547 — Transition to Post-Quantum Cryptography Standards (November 2024)** *nvlpubs.nist.gov/nistpubs/ir/2024/NIST.IR.8547.ipd.pdf* Federal transition timeline. High-risk systems by 2030; all federal systems by 2035. Identifies quantum-vulnerable algorithms (RSA, ECDSA) for deprecation. ***USE: Legal mandate basis for PQC-compliant architecture in all new NAMs data infrastructure.***
30	**Quantum Cybersecurity Preparedness Act + Executive Order 14144** *safelogic.com/compliance/pqc-standards* Federal PQC migration mandates. EO 14144 maintains PQC urgency through NSA/OMB oversight. CISA/NSA quantum-safe product categories published December 2025. ***USE: Executive authority basis for FDA/NIH PQC migration requirements.***
31	**Scrybe: PQC-Secured Audit Trail for Clinical Trial Data (PMC10629820)** *pmc.ncbi.nlm.nih.gov/articles/PMC10629820/* Peer-reviewed Hyperledger Fabric blockchain for FDA 21 CFR Part 11-compliant clinical trial audit trails. Demonstrated 100% tamper detection with negligible performance overhead. REDCap integration provided. ***USE: Direct technical precedent for Innovations 25-26. Architecture adaptable for NAMs Data Hub.***
32	**Blockchain Clinical Trial Data — Japanese Regulatory Sandbox (PMC7298640)** *pmc.ncbi.nlm.nih.gov/articles/PMC7298640/* Hyperledger Fabric blockchain validated in a government regulatory sandbox. Demonstrated data integrity preservation through a cloud server failure event. ***USE: International regulatory precedent for a U.S. NAMs blockchain regulatory pilot.***
33	**FDA TrialChain Project and DSCSA Blockchain Pilots** *flexblok.io/blog/blockchain-clinical-trial-credibility/* Documents FDA active exploration of blockchain for data integrity including the TrialChain initiative and drug supply chain pilots under DSCSA. ***USE: Internal FDA precedent demonstrating institutional readiness for Innovations 25-28.***
34	**Blockchain for FDA Submissions — HealthEconomics.com Analysis (2025)** *healtheconomics.com/leveraging-blockchain-for-enhanced-data-integrity-in-fda-submissions/*

	Proposes hash-based blockchain document fingerprinting as 21 CFR Part 11 augmentation for eCTD submissions. Identifies minimal eCTD format changes needed. ***USE: Policy basis for Innovation 27 (PQC-Signed NAM eCTD Submissions).***
35	**Frontiers in Medicine: Blockchain-Enabled QbD for Clinical Trials (2025)** *frontiersin.org/journals/medicine/articles/10.3389/fmed.2025.1546897/full* Hyperledger Fabric dual-ledger architecture (patient ledger + protocol ledger) demonstrating HIPAA-compliant design for pharmaceutical research. ***USE: Technical architecture reference for Innovation 26 CSEP Ledger dual-ledger design pattern.***

CLOSING STATEMENT

Secretary Kennedy, the March 18, 2026 package is the most significant reform to drug safety testing methodology in the history of American pharmaceutical regulation. The FDA Modernization Act 2.0 gave you the legal authority. The MAHA Commission gave you the policy mandate. The Complement-ARIE program gave you the research infrastructure. The $150 million NIH commitment gave you the funding foundation.

What remains is implementation velocity, legal durability, and data security that no adversary can compromise. The 30 innovations in this memo supply all three: accelerating the science, hardening the legal record, democratizing access, building international consensus, and protecting the entire data architecture with post-quantum cryptographic standards that will outlast any computing technology currently in existence.

Animal testing is not going away overnight, and it should not. Some studies still require it. But the default position in American drug development can and should end within this Administration's term. The tools exist. The authority exists. The public mandate exists. And now, with post-quantum secured blockchain as the trust layer, the data generated by this new paradigm will be protected permanently.

Fewer animals. Better data. Faster cures. Unbreakable data. The framework is built. Now it is time to execute.

Respectfully submitted,

Michael Freeman Liddell DC

530-651-4622

Drliddell@yahoo.com

March 21, 2026

PUBLIC COMMENT NOTE: *The March 18, 2026 draft guidance is open for public comment through May 18, 2026. Docket: FDA-2025-D-6131 at regulations.gov. Every innovation proposed in this memo is eligible to be submitted as a formal public comment and entered into the administrative record.*