Roadmap to Reducing Animal Testing in Preclinical Safety Studies

Executive Summary

This roadmap outlines a strategic, stepwise approach for FDA to reduce animal testing in preclinical safety studies with scientifically validated new approach methodologies (NAMs), such as organ-on-a-chip systems, computational modeling, and advanced *in vitro* assays. By partnering with federal agencies like NIH and VA through ICCVAM, FDA can accelerate the validation and adoption of these human-relevant methods, improving predictive accuracy while reducing animal use. This transition will enhance public health by streamlining drug development and ensuring safer therapies reach patients faster, while positioning FDA as a global leader in modern regulatory science and innovation.

Background

There is growing scientific recognition that animals do not provide adequate models of human health and disease.[1] Over 90% of drugs that appear safe and effective in animals do not go on to receive FDA approval in humans predominantly due to safety and/or efficacy issues (1). Animal-based data have been particularly poor predictors of drug success for multiple common diseases including cancer (2), Alzheimer's (3) and inflammatory diseases (4). Some medications which are generally recognized safe in humans, such as aspirin, may have never passed animal testing (5). Conversely, some compounds which have appeared safe in animal models have been lethal in human trials (5). These examples highlight basic physiologic differences between humans and other animal species.

Due to the limitations of animal testing as well as ethical concerns about animals testing, there has been increased focus within the scientific community on New Approach Methodologies (NAMs). NAMs encompass *in vitro* human-based systems, *in silico* modeling, and other innovative platforms that can collectively evaluate immunogenicity, toxicity, and pharmacodynamics in humans and provide an opportunity to improve the predictive relevance of preclinical drug testing while reducing or replacing animal use. NAMs also have enormous cost saving potential (6).

Recent legislative changes have signaled Congress is simultaneously open to regulatory innovation. In late 2022, Congress passed the FDA Modernization Act 2.0,[2] which explicitly authorized the use of non-animal alternatives (cell-based assays, computer models, etc.) to support an investigational new drug (IND) application and "remove[d] a requirement to use animal studies" for biosimilar biologics license application (BLA) (7). This landmark policy empowered FDA to accept NAMs in lieu of animal studies. Then in 2024, the Science Board to the FDA provided comprehensive recommendations on how the agency can spur adoption of scientifically validated NAMs.[3]

Public sentiment is also supportive of this transition with a recent survey finding that >85% of both Democratic and Republican-identifying adults felt that animal experiments should be phased out in favor of more modern methods.[4] Together, scientific advances and policy drivers create an opportune moment for the FDA to chart a roadmap to reduce animal testing while improving drug development.

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1 https://www.acd.od.nih.gov/documents/presentations/12142023_NAMs_Working_Group_Report.pdf
2 H.R.2565 - 117th Congress (2021-2022): FDA Modernization Act of 2021 | Congress.gov | Library of Congress
3 https://www.fda.gov/media/182478/download#:~:text=NAM%20Subcommittee%20Recommendations,all%20of%20FDA%20to%20use
4 https://pcrm.widen.net/s/qzfxtfh7bw/animal-testing-survey

Initial focus on monoclonal antibody testing

This program is intended to begin with monoclonal antibodies (mAb) as a promising area for reducing animal use in preclinical safety testing, and then will expand to include other biological molecules and eventually new chemical entities and medical countermeasures. Current FDA requirements for mAbs mandate GLP-compliant repeat-dose toxicity studies (often 1–6 months duration) in animals, alongside assessments of pharmacokinetics (PK) and safety pharmacology. Anti-drug antibody formation (immunogenicity) is monitored because animals often mount immune responses to human mAbs, which can alter exposure and confound toxicity interpretation. However, animal immunogenicity is not predictive of human immunogenicity due to interspecies differences in immune systems (6). In addition to inherent biological differences, stress of laboratory life and use in research can impact immune function, inflammatory responses, metabolism, and disease susceptibility and progression.[5] Moreover, some safety risks may go undetected in animals – a notable example is the mAb TGN1412, which caused a life-threatening cytokine release syndrome in human volunteers despite appearing safe in preclinical monkey studies. That tragedy highlighted the limitations of animal models for certain immune-activating mAbs and spurred efforts to develop *in vitro* assays to better predict human-specific responses (7).

Beyond scientific shortcomings and ethical issues, animal testing of mAbs poses practical challenges. The cost of drug development can vary by therapeutic class, with a market report noting the cost to develop a mAb at $650-$750 million and taking up to 9 years.[6] Typical mAb development programs typically use 144 non-human primates (NHPs).[7] In recent years, costs of NHPs have skyrocketed, up to $50,000 per NHP.[8] The time and cost of long-term animal studies slow down delivery of new therapies to patients. Indeed, a majority of drug development failures are due to lack of efficacy or unexpected safety issues that were not evident in animal tests (1), meaning that issues for humans were only realized in clinical trials or after approval. As more predictive methods are integrated into decision-making earlier, companies will not only save the direct costs of avoiding certain nonclinical animal use, but they will also be positioned to make better business decisions by making more informed go/no go decisions regarding which therapeutics to advance, which could ultimately lower drug costs.

New Approach Methodologies (NAMs)

NAMs offer the tools to assess safety, efficacy, and pharmacology of drugs and therapeutics *without* traditional animal models. NAMs include *in vitro* human-based systems such as organs-on-chips, "*in silico"*, or computer-based modeling, as well as other innovative platforms that can collectively evaluate immunogenicity, toxicity, and pharmacodynamics with high relevance to human biology. The FDA and the broader scientific community recognize NAMs as a means to obtain "faster and more accurate human risk assessments" while reducing animal use (8). Below is an overview of key NAM categories and their applicability to drug development:

In Vitro Human-Derived Systems (Organoids and Microphysiological Systems)

Advances in tissue engineering have led to organoids and microphysiological systems (MPS) (often called "organs-on-chips"). These systems use human cells to recreate miniature organ units or even interconnected multi-organ networks. Organoids are self-organizing cell cultures (e.g. liver organoids, gut organoids) that model native tissue architecture and function. Organ-on-a-chip devices go a step further by incorporating

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

[6] https://www.labmate-online.com/news/news-and-views/5/frost-sullivan/market-report-therapeutic-monoclonal-antibodies-in-europe/22346

[7] https://nc3rs.org.uk/our-portfolio/reducing-animal-use-monoclonal-antibody-development

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

microfluidic flow, mechanical forces, and multi-cell type co-cultures on a bioengineered chip, emulating the *in vivo* environment. For example, a human Liver-Chip can co-culture hepatocytes with non-parenchymal cells under perfusion, displaying liver-like metabolism and responses. These platforms maintain human-specific biology that animals lack, allowing detection of effects that only manifest in human tissue.

Notably, microphysiological systems can be as predictive (or more predictive) of human responses than animal tests (9). The drive to eliminate animal testing in cosmetics led to the first successes of this approach – e.g. *in vitro* human skin models that supplanted rabbit skin tests – and now human-based MPS devices exist for liver, heart, lung, kidney, and other organs. A recent example is a Human Liver-Chip, which was recently evaluated for its ability to predict drug-induced liver injury (DILI) and accepted into FDA's Innovative Science and Technology for Advancing New Drugs (ISTAND) pilot program. In a validation study, the Liver-Chip correctly identified 87% of hepatotoxic drugs that caused liver injury in patients (10).

In monoclonal antibody safety, organoids/MPS can evaluate target-specific and off-target effects in a controlled human microenvironment. For instance, if a mAb may cause liver injury via an immune-mediated mechanism, a Liver-Chip with integrated immune cells could detect cytokine release or hepatocyte damage. If a mAb has cardiovascular risks (e.g. binding an off-target in heart tissue), a cardiac tissue chip or human stem-cell derived cardiomyocyte assay can screen for pro-arrhythmic effects. These models also permit real-time monitoring of functional endpoints (e.g. electrophysiology, enzyme release, biomarkers) that parallel clinical safety markers. Many mAbs have immune-related effects, so human immune organoids (like lymph node or spleen organoids) and blood-on-a-chip systems with circulating immune cells can be used to test for cytokine release, T-cell activation, or other immunotoxicity. Indeed, after TGN1412, researchers developed *in vitro* cytokine release assays (CRAs) using human blood and immune cells to screen therapeutic antibodies for pro-inflammatory activity (7). Such assays, including whole-blood and peripheral blood mononuclear cell (PBMC) models, can now be employed to identify any mAb that might trigger a dangerous cytokine surge, thereby adding a crucial safety net that animal tests struggled to provide. Additionally, multi-organ "human-body-on-a-chip" setups can simulate pharmacodynamic effects systemically – for example, connecting liver and tumor tissue chips with an immune compartment to study a cancer immunotherapy mAb's on-target tumor killing and off-target organ toxicity in one human microphysiological model. By using *human* cells, these systems avoid species differences and can reveal toxicological effects that are more relevant to patients.

In Silico Tools and Computational Modeling

In silico approaches are another pillar of NAMs. Computational modeling, artificial intelligence (AI), and machine learning (ML) can leverage existing data to predict safety, immunogenicity, and pharmacokinetics, reducing the need for new animal experiments. Key *in silico* tools include:

- **Physiologically-Based Pharmacokinetic (PBPK) Modeling:** PBPK models are mathematical simulations of drug ADME (Absorption, Distribution, Metabolism, Excretion) using species-specific physiology. They have become integral in small-molecule drug development and are increasingly applied to biologics. FDA may review PBPK simulations to inform first-in-human dosing and to justify waiving animal studies that would normally serve that purpose. As PBPK models are refined, they can also predict how differences between patients (e.g. body weight, disease state) might affect a drug's pharmacokinetics, further enhancing safety margins.

- **ML and AI Predictive Models:** Machine learning algorithms can be trained on drug sequence features, structural motifs, and known clinical outcomes. Recently developed ML models analyze the amino acid sequence of an antibody's variable region to predict whether the mAb is likely to have high or low immunogenicity (11). Such tools can flag problematic sequences early guiding engineering to "de-risk" the product before it ever enters an animal or human. Machine learning models are also being explored to predict toxicities (like acute systemic toxicity, off-target binding, or cytokine release potential) by learning patterns from molecules that caused certain adverse events (12).

- **Quantitative Systems Pharmacology (QSP) and Modeling of Biological Pathways:** QSP models combine computational biology and pharmacology, simulating how a drug interacts with complex human biological networks. For example, a QSP model of an autoimmune disease could simulate how an antibody modulates inflammatory pathways, helping to predict efficacious dose ranges and potential toxic outcomes (such as over-suppression of the immune system). These models could reduce reliance on animal disease models by providing a *virtual human* on which to test "what-if" scenarios.
- **Bioinformatics and *In silico* Off-target Screening:** Using databases of human proteins and AI, one could screen a product's sequence for any unintended targets (such as cross-reactivity to human tissues). *In silico* tools can analyze whether the drug might bind to similar epitopes in the human proteome, highlighting potential safety concerns that would traditionally be checked via animal tissue cross-reactivity studies or broad receptor binding panels.

Overall, *in silico* NAMs may act as powerful adjuncts or replacements for animal studies by predicting human-relevant outcomes through data and modeling. They are rapid, cost-effective, and can integrate vast amounts of existing knowledge – for instance, an AI model might instantly compare a new drug to hundreds of prior ones to assess risk, something impossible with animal testing alone. Importantly, as regulators gain confidence in these tools (through retrospective validation and prospective pilot use), they could be formally adopted to reduce or replace specific animal tests.

Thresholds will need to be developed and modified for when animal testing can be reduced or eliminated. This should be continuously updated as modeling programs are augmented with more data, validated and improved.

Other Innovative Platforms

Beyond complex *in vitro* and computational *in silico* categories, a variety of innovative approaches can also contribute to a non-animal safety testing ecosystem:

- **Ex vivo Human Tissues:** Advances in organ donation and tissue preservation allow scientists to test drugs on actual human tissues. For example, donated human organ slices (liver, heart, etc.) maintained in culture can be exposed to a drug to look for localized toxic effects or immune cell infiltration. While limited in lifespan, such ex vivo systems use native human tissue architecture, complementing engineered organoids.
- **High-Throughput Cell-Based Screening:** Robotic high-content screening using panels of human cells (including induced pluripotent stem cell-derived cells from diverse genetic backgrounds) can profile the effects of a product on many cell types. This can reveal off-target cytotoxicity or functional changes in a broad, human-relevant manner, something traditionally assessed with multi-species animal testing.
- **Microdosing and Imaging in Human Volunteers:** In certain cases, microdosing studies in humans can yield early pharmacokinetic and distribution data via PET imaging. This is not a routine approach for biologics yet, but as modeling and microdose safety are established, it could provide direct human data in place of animal distribution studies, with minimal risk.
- **Refined *In Vivo* Methods (for transition):** As the field reduces reliance on animal testing, interim steps can involve refined *in vivo* methods. For instance, using humanized transgenic can reduce animal numbers and pain (these still involve animals, but fewer, or with less severe procedures).

Each NAM described addresses one or more aspects of what animal studies currently provide, often with enhanced human relevance. To minimize animal testing, it will be essential to use an integrative strategy: for example, a combination of a human organ chip for toxicity, a PBPK model for PK, and an AI immunogenicity predictor might together cover the same ground as a traditional whole-animal study, but with greater accuracy and ethical acceptability.

Implementation of reduced toxicity testing in animals at the FDA in the next 3 years

1. **Explore Pre-existing International Data:** Determine if drug toxicity data from humans already exists in countries where the compound has been approved. If international data exist, drug and biologic manufacturers will be encouraged to collect, analyze and provide these data, which the FDA will now consider in IND applications. By default, it will *not* be necessary to submit additional human data to the FDA if the product has been approved in a different country with similar regulatory standards unless the data are felt to be insufficient by FDA reviewers. If data are felt to be insufficient, FDA reviewers will outline specifically where uncertainty lies and what type of additional safety information they would like to see.

2. **Encourage sponsors to submit NAM data** in parallel with animal data to build a repository of experience. For example, communicate with manufacturers that we welcome organoid or *in silico* study results in IND/BLA packages as supportive data. Ensure companies understand that less animal testing will be required if NAM data are validated. Offer regulatory relief (e.g. fewer animal study replicates) to those who do so. Identify a few pilot cases where, based on strong rationale, an animal study is waived in favor of a NAM. For instance, if a mAb targets a human-specific receptor and the only possible animal model is a transgenic mouse, FDA could allow a sponsor to substitute a battery of human *in vitro* tests or MPS plus a PBPK model instead of the transgenic mouse study. Monitor the outcomes of those programs closely (through clinical trial phases) to verify safety was not compromised.

3. **Develop an open-access repository with a comprehensive collection of international drug toxicity data from animals and humans.** No comprehensive database containing animal and human toxicity data currently exists. Databases are either limited to countries or international collaborations focusing on publicly available toxicity testing information. One example is the Integrated Chemical Environment,[91] containing legacy animal studies in addition to curated data from the US Tox21 program, which has generated toxicity measurements of thousands of chemicals (13,14). This program has led to models integrating in vitro assays that have been found to be as reliable as animal models and in some cases superior (15), but can be substantially augmented with other private and/or international datasets. The FDA will plan to expand the Tox21 program and combine other existing international databases to create a comprehensive database to be utilized in toxicity modeling efforts. The FDA will also plan to partner with the National Toxicology Program (NTP) to expand and validate this database.

4. **Reduce the routine 6-month primate toxicology testing for mAbs** that show no concerning signals in 1-month studies plus NAM tests to three months. Notably, first-in-human enabling study, suggesting that shorter or fewer studies could suffice in most cases (15). Adopting a *data-driven paradigm* (such as a weight-of-evidence model) could allow FDA to confidently drop these extended animal studies for many mAbs.

5. **Reduction in animal toxicity testing timeframes for other drug categories:** Reduced duration of animal toxicity testing may be implemented for additional drug and biologic compounds. This will be initiated be based on all relevant prior clinic information about the compound or class of compounds and augmented by modeling in the case of low toxicity risk prediction. The FDA may implement a randomized study of new drugs evaluating costs and benefits (human, animal and economic) of 3 months of animal testing augmented with AI vs 6 months of animal testing with AI vs 3 or 6 months of animal testing alone to evaluate the benefits and costs of this initiative.

[9] Integrated Chemical Environment (ICE)

6. **Changes in toxicity testing will be tracked and quantified** on a bi-annual basis and will include, to the extent feasible:
   (1) Animal testing hours and cost by species
   (2) Toxicity testing costs per IND
   (3) Economic analysis of safety signals identified through NAMs/modeling vs through animal testing
   (4) Changes in toxicity testing costs over time
   (5) Rates of novel toxicities first identified in humans or not until post-marketing surveillance
   (6) Time from IND to full approval

In the **long-term (3-5 years)**, FDA will aim to make animal studies the *exception* rather than the norm for pre-clinical safety/toxicity testing. By this stage, validated NAMs could cover all critical areas, and FDA requirements can shift to a NAM-based default. Animal tests might only be considered if a specific scientific question cannot yet be answered by NAM (and even then, only the minimal animal use necessary, with strong justification). Ultimately, the vision is that no conventional animal testing will be required for mAb safety, and eventually all drugs/therapeutics – instead, a comprehensive integrated NAM toolbox (human cell models + computational models) will be the new standard.

Scientific and Technical Steps for FDA Adoption of NAMs

Transitioning from animal-based testing to NAMs for safety will require careful planning, robust science, and collaboration. Below is a stepwise list of specific actions the FDA is considering for validation and integration of NAMs into their regulatory process:

1. **Map Critical Endpoints and Use Cases:** FDA should begin by identifying the key safety and efficacy questions for drugs and biologics where NAMs could replace or augment animal data. These include acute toxicity, chronic toxicity and organ injury, pharmacokinetics and bio-distribution, immune responses and pharmacodynamics (target engagement and functional effects). For each area, perform a gap analysis of current methods. Prioritizing such gaps helps focus on where NAMs will have the most impact and urgency.

2. **Support Targeted Development of NAM Technologies:** FDA (through research collaborations with NIH and other venues) should invest in the development of NAM models. This could involve:

   a) Developing organotypic models for drug toxicity.

   b) Creating an open-access comprehensive database of drug and biologic toxicity data from animals and humans to improve model training data.

   c) Developing ways to study the efficacy and costs of NAMs vs more traditional models of animal testing.

   d) Developing studies to determine appropriate thresholds for reducing or eliminating animal testing based on predetermined level of likelihood and predicted severity of toxicity.

3. **Establish Validation and Qualification Pathways:** It will be critical to continuously rigorously validate NAMs to build confidence in their reliability. Possible approaches include:

   a) **Retrospective analyses:** Gather data from past (preferably well-known and well-defined) drug toxicities and determine the accuracy with which NAM (e.g. an organ chips, ML models, integrated strategies) would have predicted the human outcome. This can be compared with animal study predictiveness for a wide range of drug and biologic classes. All research projects should be preregistered and published in a timely manner.

b) **Prospective validation trials:** In collaboration with stakeholders, perform parallel testing of new drugs products in both animals and NAM systems, to directly compare accuracy, financial costs as well has harms to both humans and animals. For example, test a novel cancer therapy with organ-on-chips, computer modeling and in vivo alone or combined, and see which method/s best correlate with clinical effects both in clinical trials and in subsequent real-world data.

c) **Reproducibility and standardization:** Work through consortia (perhaps via ICCVAM, discussed below) to have multiple independent labs test the same drug product in a given NAM to ensure reproducibility. Develop standardized protocols for these methods so that results are replicable across laboratories.

d) **Benchmark against human data:** Ongoing validation studies should be implemented that assess how well NAM predictions align with human clinical trial and post-marketing findings.

e) **NAMs-based prospective post-marketing studies:** When appropriate use NAM predictions for prospective post-marketing studies of side effects.

To formalize acceptance, FDA could employ its **"Drug Development Tool" (DDT) Qualification programs** (like the ISTAND pilot) for NAMs. This provides a pathway where method developers submit qualification plans to FDA, and FDA reviews the evidence that the NAM is fit for a specific Context of Use. Once qualified, any sponsor could use that NAM in an application with confidence that FDA will accept the data. Creating clear contexts of use for NAMs is crucial; the qualification requirements will vary by intended use and defining this upfront guides the validation process (15).

4. **Develop Regulatory Guidance and Standards:** FDA will update or create guidance documents that articulate how NAMs can be used in various development programs. This might include:

a) **Guidance on replacing specific animal studies:** e.g. "If an appropriately validated microphysiological system or *in vitro* assay is used to assess XYZ toxicity, a second-species chronic toxicity study may not be required." The guidance would enumerate what data/validation is needed to justify such a replacement.

b) **Technical guidance on conduct of NAMs:** to ensure industry runs these new assays to high standards (analogous to GLP). For example, specify expectations for tissue chip stability, cell characterization, or computational model verification when used in regulatory submissions.

c) **Case examples:** Provide examples in guidance of how sponsors can incorporate NAM data alongside or in place of animal data in their IND/BLA submissions. Clear regulatory expectations will encourage sponsors to invest in NAMs.

Updating international guidelines is also important. FDA can propose revisions to ICH guidelines (e.g. ICH S6) to reflect NAM usage, ensuring global regulatory alignment so that companies do not face different rules in different regions. An ultimate vision could be an ICH guideline on New Approach Methodologies for Drugs and Biologics Safety Testing, which FDA can champion once enough evidence has been generated.

5. **Training, Communication, and Culture Change:** For this transition to succeed, FDA must ensure its reviewers and scientists are well-versed in NAM technologies and open to novel types of evidence. The Agency will commit to:

a) Provide training workshops for review staff on interpreting organ-on-chip data, understanding AI model outputs, and analyzing in vitro-in vivo extrapolation from PBPK models. Building this expertise will increase comfort and consistency in reviewing NAM-based submissions.

b) Foster a culture that recognizes the scientific merit of NAMs. Management can explicitly encourage consideration of NAM data and celebrate successful cases where a non-animal method provided a key insight or decision-enabling information, while maintaining a critical eye on potential areas of weakness where NAMs may not yet be sufficient and need further development.

c) Maintain open dialogue with industry, academia, and NGOs. For instance, hold public meetings or advisory committee discussions on NAM advances in drug and biologic development, and incorporate external expert feedback.

d) Communicate to sponsors via guidance and Q&A documents how they can engage FDA early (e.g. in pre-IND meetings) to discuss proposals for using NAMs. Clear communication will alleviate uncertainty and spur more sponsors to utilize these methods.

6. **Monitor Outcomes and Iteratively Refine**: As NAMs become integrated, FDA should establish metrics to monitor their performance in practice (e.g. correlation of NAM predictions with clinical trial safety data). Learn from any unexpected outcomes – if a safety issue arises in humans that NAMs did not predict, analyze why and determine how models might be improved. Likewise, track efficiency gains (e.g. reduction in drug development time, fewer animals used) as measures of success. This feedback loop will allow the roadmap to be adjusted and improved continually.

By executing these steps in collaboration with other federal partners, such as the NIH, the FDA will build a solid scientific foundation to reduce and, when appropriate, entirely replace animal tests with NAMs.

Interagency Coordination through ICCVAM

The FDA will collaborate with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), which provides a ready-made platform for partnership with other federal entities like NIH and the Department of Veterans Affairs (VA). ICCVAM is a committee of 18 U.S. agencies (including FDA, NIH, DoD, EPA, VA, and others) established to "work together to develop and evaluate new, improved, and alternative test methods and strategies". Leveraging ICCVAM can accelerate progress by pooling expertise, data, and resources across government.

How FDA can partner via ICCVAM and related interagency initiatives:

- **Coordinated Validation Efforts:** Through ICCVAM, FDA can enlist multiple agencies' laboratories in multi-site validation studies of NAMs for drug and biologic safety. For example, NIH's Interagency Center for the Evaluation of Alternative Methods (NICEATM; the support organization for ICCVAM) has significant experience in method validation, and can assist in designing validation studies, statistical analyses, and independent evaluation of a new test's performance. If the FDA identifies a promising organoid model, ICCVAM could establish a working group to validate it, with participants from across the federal government and support from NICEATM. This collaborative validation not only shares the workload but also adds credibility – a method validated by multiple agencies is more likely to gain broad acceptance.

- **Funding and Research Support from NIH:** The National Institutes of Health can direct funding towards NAMs that FDA deems priority. A pertinent example is the Complement Animal Research in Experimentation (Complement-ARIE) program, which supports the development of combinatorial NAMs for critical biomedical research and regulatory questions. The NIH and FDA could also co-sponsor challenge grants or prize competitions for developing NAM solutions to specific problems (such as a computer model predicting antibody biodistribution in humans). The VA might contribute funding or clinical data for projects that have dual benefit for veteran health research and regulatory science.

- **Shared Data and Databases:** Under ICCVAM's coordination, agencies can compile shared databases of toxicology and immunogenicity that include both animal and human data from various sources. FDA's vast repository of historical IND/BLA data (de-identified/encrypted as needed) combined with NIH's research data could be a treasure trove for training AI models or doing retrospective NAM analyses. The creation of a **central database for validated NAMs,** called the Collection of Alternative Methods for Regulatory Application (CAMERA), is being led by ICCVAM and is already underway, with a beta version expected mid-2025. This will be used until a more comprehensive international database can be developed. This initiative will include an FDA-NIEHS partnership with the National Toxicology Program (NTP).

- **ICCVAM Workgroups and Outreach:** FDA can take a leadership role in ICCVAM workgroups specifically focused on safety testing of drugs and/or biologics using complex in vitro models and other NAMs. ICCVAM also hosts annual public forums and Communities of Practice webinars – FDA can use these to communicate its NAM roadmap progress and engage external stakeholders. ICCVAM's 2025 Communities of Practice webinar will discuss ongoing work in complex *in vitro* models, including NAM-based case studies.

- **Cross-Agency Training and Expertise Exchange:** FDA scientists can collaborate with NIH intramural researchers who are pioneers in organs-on-chips, with VA researchers exploring human-based models for trauma or rehabilitation or NTP researchers on testing and methods validation. Short-term staff exchanges or joint training sessions (e.g. FDA reviewers visiting a NIH tissue chip lab, and NIH scientists learning about regulatory review processes) will foster mutual understanding. This ensures the methods developed meet regulatory standards and that FDA is intimately familiar with the science behind them.

- **Public-Private Partnerships via Federal Consortia:** ICCVAM isn't limited to just government agencies; it often engages with industry, academic, and NGO stakeholders as observers or through sponsored workshops. FDA can encourage ICCVAM to organize public-private partnership forums, (initially on mAb testing and developing a more comprehensive and open access toxicity database), following models such as the IQ Consortium's Microphysiological Systems Affiliate, a collaboration among pharmaceutical companies and FDA scientists that was formed to tackle MPS evaluation for drug development.

In essence, ICCVAM provides the mechanism for a unified federal strategy. By partnering with NIH, VA, DoD and others, FDA can harness a wide pool of scientific innovation to validate NAMs faster than it could on its own. Such collaboration also presents a united front to the public and stakeholders that federal agencies are committed together to reducing animal use and advancing human-centric science.

Recommendations and Policy Considerations

Building on the above, the FDA leadership intends to combine scientific rigor with policy actions, minimizing animal testing in preclinical safety evaluation:

- **Develop Clear Guidance and Regulatory Flexibility:** Issue new guidance (or revise existing ones like ICH S6(R1)) that explicitly allows for alternative methods. In the interim, use mechanisms like case-by-case waivers or exemptions to permit sponsors to omit animal studies if they provide adequate NAM data. For example, FDA could announce that for products meeting specific criteria, a single species study is sufficient if accompanied by an orthogonal NAM dataset addressing the same safety questions, or in other cases an exclusively NAM-based approach may be warranted. Such policy signals will encourage wider trial of NAMs in submissions.

- **Incentivize Sponsors and Promote Success Stories:** Consider incentives for companies that utilize NAMs – for instance, fast-track meeting requests and regulatory reviews, or publish case studies of successful FDA approvals that minimized animal testing. Publicize when FDA approvals were achieved with novel approaches (similar to how FDA highlights first-in-class approvals, it could highlight "first

approval with no animal testing" as a milestone) and highlight the benefits (decreased cost, higher accuracy, less harm to animals, etc). This positive reinforcement can shift industry practices. Over time, as animal testing becomes seen as optional rather than mandatory, industry will move away from the old defaults.

- **Ensure Scientific Rigor and Continuity:** While pursuing replacement, maintain a focus on scientific validity. FDA must assure that any new method is equal or superior to the animal test it replaces in protecting patients. By following modern validation principles (15), FDA can make this transition without increasing risk. In fact, by using human-relevant models, safety for patients should improve. FDA should continuously update its approach based on effects on valuable outcomes.

- **Legislative and Funding Support:** Work with lawmakers to secure funding (perhaps via FDA's budget or NIH collaborations) specifically earmarked for NAM validation and implementation. If needed, seek further legislative reinforcement – e.g. establishing deadlines after which certain animal tests cannot be required if alternatives exist (similar to how EU banned cosmetic animal testing). Although FDA has authority to use alternatives, increased support and oversight means Congress can be kept informed of progress (consistent with the proposed FDA Modernization Act 3.0).

- **Global Leadership and Harmonization:** Use FDA's influence in international regulatory forums to drive a global shift. Propose discussions at ICH for incorporating NAMs into guidelines for biologics. Collaborate with EMA, PMDA, and others on joint workshops or qualification projects (perhaps an international validation of a particular organ chip). This will help sponsors have confidence that NAM-based strategies will be accepted worldwide, not just in the US, which is critical for adoption. Work on collaborative international initiatives that are not limited to within the FDA. The ultimate vision is a global regulatory environment where animal testing for biologics is largely obsolete, replaced by a new standard toolbox of approved NAMs.

Conclusion

This scientific roadmap lays out an initial strategy for FDA to reduce and replace animal testing in preclinical safety assessment of drugs and biologics and will be refined based on feedback provided by FDA stakeholders. By combining cutting-edge *in vitro* systems, advanced *in silico* modeling, and robust validation efforts – and by working collaboratively across government and industry – the FDA can ensure that drug development becomes more ethical, more efficient, and more predictive of human outcomes. Patients will benefit from safer and faster-to-market therapies, animals will be spared from testing, and the science of drug development will enter a new era aligned with 21st-century technology. This plan aligns with congressional directives and global trends, positioning FDA as a leader in regulatory science innovation. Implementing this roadmap will demonstrate FDA's commitment to embracing scientific advancements, which are ethical, reduce costs and improve human health.

Citations

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