Potential Approaches to Drive Future Integration of New Alternative Methods for Regulatory Decision-Making

A Report to the Science Board to the Food and Drug Administration from the New Alternative Methods Subcommittee

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1. Executive Summary

The scientific community, along with FDA scientists, are exploring emerging technologies that are classified as **N**ew **A**lternative **M**ethods (NAMs), sometimes referred to as New Approach Methodologies. NAMs are regarded as a possible way to drive faster and more accurate human risk assessments of compounds that FDA regulates (e.g., as drugs, food, cosmetics, and others) while also holding promise to facilitate the reduction of the use of animals for regulatory decisions, such as those made by FDA product centers. NAMs include a variety of technologies, methodologies, and approaches such as in vitro tests, in silico computational models, biomarkers, and modified in vivo assays that can fill critical information gaps and build confidence for their use in regulatory decisions.

Industry innovators have adapted some NAMs in their discovery efforts for the purpose of screening and identifying compounds to put forward as markers for regulatory decisions for marketing approvals. In most cases, NAMs help screen or rank order compounds for specific biological responses or contribute important mechanistic and investigative insights addressing specific cell, organ, or molecular questions related to efficacy and safety. The scope of the FDA strategy is not to address the discovery and screening opportunities conducted by industry, but specifically to bring focus to opportunities for deployment of NAMs toward current and future regulatory decision-making for those compounds put forward for public exposure. Importantly, note that technical limitations to current NAMs exist and, that today, no assays fully capture the critical hazard endpoints for assessing all currently existing human or animal organ systems; therefore, NAMs cannot fully eliminate the use of integrated physiological systems such as in animal and human trials. While NAMs represent promising tools for decision-making, they are, in most circumstances, currently best used in conjunction with traditional methods and not as stand-alone solutions for hazard identification or human risk assessment. However, this position will continue to evolve over the coming years and decades as some areas show promise for faster opportunities and rates for adoption than others – such as in vitro "barrier models" for cosmetics or food testing, (e.g., drugs).

FDA recognizes that important opportunities exist to expand the consideration and qualification of NAMs for regulatory decision-making and to reduce the dependency on animal models. Over time, we expect that NAMs could impact regulatory decision frameworks by providing more precise information around potential effects of new compounds in humans. In doing so, NAMs could contribute to faster regulatory decisions, reduce dependency on animal models, and aid mechanistic understanding for human benefit-risk. Therefore, at this time FDA requested advice from the Science Board to help determine the best approach(es) to build confidence and experience with NAMs to inform future use in regulatory decision-making. The Science Board, in response to the FDA charge, developed this set of recommendations:

NAM Subcommittee Recommendations

1. Create a central NAMs office that provides an agency-wide strategy to coordinate and drive effective and efficient prioritization and implementation (execution) of NAMs. This will "signal" to critical stakeholders and partners FDA's commitment and seriousness to drive change with the adoption of NAMs, as appropriate. This includes assuring impactful communication, focus, and driving effective partnerships.

2. Determine effective metrics that demonstrate the impact of ongoing FDA investments in NAMs (wider FDA).

3. Create a uniform FDA framework for qualifications of NAMs (wider FDA).

4. Establish a transparent and scientifically rigorous review process for incoming product applications that rely on NAMs to demonstrate efficacy and/or safety.

5. Identify and invest in high-impact NAMs initiatives to fully execute that will aid in regulatory decisions.

6. Compile a central NAMs database for all of FDA to use.

2. Introductory Material

NAM Subcommittee Charge Provided by FDA:

Goal

FDA seeks input from the Science Board on how the agency can enhance its existing approaches to support the development, qualification, and implementation of alternative methods for regulatory use that can:

- Replace, reduce, and refine animal testing (i.e., the 3Rs)
- Improve predictivity of nonclinical testing

Background and Questions

Animal testing plays a critical role in gaining important knowledge needed to thoroughly evaluate the health risks of FDA-regulated products or develop effective new products that reduce human and animal suffering. FDA has a long-standing commitment to promote the development and use of new technologies to better predict human and animal responses to substances relevant to its regulatory mission. FDA's current regulatory framework permits and encourages the use of new alternative methods to animal testing, as described in regulations and guidance. FDA supports alternative methods backed by science and that produce scientifically valid data to meet the regulatory need. As FDA and the scientific community continue to implement the 3Rs, recognize the current state of the science related to alternative methods that may provide tools that complement or possibly eliminate specific tests, and acknowledge that the need for considerably more research and development tools that might replace the battery of animal studies that currently support a multitude of safety and efficacy assessments. As the science supporting non-animal alternative methods continues to develop and advance, FDA seeks input on the following questions:

1. FDA is interested to spur the adoption of scientifically valid alternative methods for regulatory use. What factors should FDA consider in pursuing this goal? What measures are necessary to ensure confidence in these data? What steps are necessary to ensure adoption of these new alternative methods?

2. FDA regularly engages the external scientific community to advance the Agency's public health mission. What additional types of collaborations and partnerships, across national and international industry, academia, and government partners should FDA pursue to facilitate adoption of scientifically valid alternative methods in regulatory context of use? Are there recommended strategies for prioritizing and coordinating such collaborations and partnerships? For international regulatory counterparts, are there additional opportunities for information sharing?

3. FDA has product development tool for both existing drugs/biologics and medical devices qualification programs and programs under development, that can facilitate qualification of alternative methods. How can we further clarify and/or enhance existing programs and

inform developing programs to help ensure submission of high-quality alternative methods data for regulatory contexts of use?

4. FDA seeks input from the subcommittee that will assist stakeholders developing alternative methods for regulatory use. This might include identifying specific safety or development areas of focus, methods for assessing credibility of specific types of alternative methods, or what to include in regulatory submissions. Are there other recommendations from the subcommittee and how would the subcommittee recommend prioritizing?

5. FDA has provided information on its website stemming from Agency-wide scientific working groups (e.g., FDA's Predictive Toxicology Roadmap by FDA's Toxicology Working Group and Advancing Alternative Methods Report by FDA's Alternative Methods Working Group). What other mechanisms should FDA explore to ensure its efforts are readily understood to effectively communicate a cohesive and comprehensive strategy to advance the qualification and adoption of alternative methods for regulatory use? What mechanisms can best communicate FDA's continued progress on this topic?

Process

The Science Board convened a subcommittee consisting of standing members of the Science Board and subject matter experts in disciplines at the intersection of risk assessment and laboratory, computational, or preclinical/clinical science applicable to the context of the regulatory decisions for which FDA is accountable.

Listed below, members of the NAMs subcommittee generated the recommendations included in this report. The committee convened in September 2023 to conduct research by reviewing literature and other public domain documents. To learn about FDA strategies and research, the committee conducted interviews and discussions with FDA staff and representatives. The committee members worked through a combination of independent research along with regular committee deliberations, including a 2-day face-to-face meeting, to inform their final recommendations and the drafting of this report. This work culminates in the presentation of this report to the full Science Board, FDA leadership, and the public on October 7, 2024.

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FDA Center Context for NAMs

FDA scientists and administrators play an important role in protecting the health of the citizens of the United States and around the world via global harmonization/coordination. The Agency is complex and has a wide remit across several different product centers that all share this same goal of protecting the public but regulate different products under different decision/statutory

radiation-emitting products, and tobacco.

Depending on the type of product, FDA may take, in some cases, a "proactive" or "pre-market" assessment of product efficacy and safety and make a careful data assessment before the decision to permit approval to move forward to commerce. For these cases, the ability to reduce uncertainty and improve confidence in product performance, through leveraging human test systems, *in vitro* or *in silico*, has the potential to improve the risk assessment process by eliminating gaps created by trying to extrapolate from one species to another (e.g., animals to humans). For product centers with pre-market regulatory approval, the burden for testing lies with the sponsor; and FDA reviewers need to have the expertise to understand and judge the integration of these endpoints into the overall assessment of efficacy and/or risk. However, in several other product examples, FDA needs to be able to respond quickly to potential safety or other threats raised in the market. For example, some product centers (e.g., foods, cosmetics) do not conduct pre-market approval assessment, but they face a need to rapidly discern severity of risk when a higher number of cases of adverse events associated with material or specific concerns are raised regarding a compound already on the market. For these cases, speed is of the essence, and *in silico* and cell-based models have the potential to provide rapid outputs that can produce informative insights for specific contexts of use. In these cases, the burden is on FDA to conduct investigative testing to determine and inform regulatory action. Though it is not yet possible for NAMs to cover the full array of all human target organ systems, they can still be deployed in certain regulatory decision frameworks for both the pre-and-post-market product assessments.

Through the investment being made in internal research programs and in cross-sector partnerships, FDA is demonstrating its long-standing commitment to promote the development and use of new technologies to better predict human and animal responses to substances relevant to its regulatory mission. Table 4 (Appendix) summarizes the current FDA product Centers and, at a very high level, the scope of their decisions, including examples of their emerging NAMs approaches.

Current FDA Regulations Requiring Animals for Decision-Making: Opportunities for NAMs

A fairly large number of FDA and global guidelines exist that dictate the path to market approval for products that FDA regulates. The current regulatory framework permits and encourages the use of NAMs to animal testing, as described in regulations and guidance. For individual product decisions, the contribution of alternative approaches typically contributes "weight of evidence" to other supplemental information specific to the submission. However, it is these individual precedents, through thoughtful cross-sector lesson sharing along with the opportunity to more deeply examine this collection of guidance, that provide the specific opportunities for FDA in terms of looking at prioritization of the most and potentially impactful approaches to minimize the use of animals through deployment of validated NAMs. Again, reviewing these these guidelines makes clear that a number of them require testing in cross-organ complex systems and therefore there may not represent a "quick win" to replace with an alternative approach. However, in other

cases with very specific needs, these may provide the first place FDA can accelerate

backed by science that produce scientifically valid data to meet the regulatory need.

FDA is not unique in its desire to pursue NAMs. International agencies and other sectors and government agencies, such as the U.S. Environmental Protection Agency (EPA), use NAMs approaches today. Through scientific community and partnership, learnings and advances can benefit multiple stakeholders (Table 1). FDA should continue to use existing predictive and validated systems while individual product Centers continue to partner and develop the science and context for their decisions for regulatory approvals. Examples of newer and complementary methods, largely already available in some of FDA's Centers, include the following:

- Systems biology (evaluating multiple aspects of cell and tissue responses to study the whole organism)
- Engineered tissues (using scaffolds and cells to form biologically active tissues)
- Artificial Intelligence (using computer [in silico] approaches)
- Alternative organisms such as Zebrafish and *C. elegans*
- Microphysiological systems (MPS), including organs-on-chips

FDA has also accepted approaches that reduce the number of animals used in required protocols and has illustrated support of guidances such as ICH S6 requiring that only testing of only relevant species, waiver options for reproductive toxicology (ICH S5), and carcinogenicity testing (ICH S2), and elimination of chronic toxicology study requirement for oncology indications (ICH S9). In addition, FDA has explored options to support reduction of animals in study using "virtual control groups" (Golden, E. *et al.,* 2024). Table 5 (Appendix) captures the breadth of opportunity for use of NAMs in regulatory decision-making.

Current state of existing 3Rs frameworks and principles for NAMs in FDA

FDA supports the principles of the "3Rs," to replace, reduce, and/or refine animal testing when feasible to support regulatory needs. NAMs have the potential to provide more timely and predictive information to assess certain aspects of FDA-regulated products while also replacing, reducing, and/or refining animal testing. Considerable efforts are underway to better understand how and where NAMs can be utilized within FDA's regulatory framework and authority. For example, the Agency has issued numerous documented activities dealing with the subject including those listed in Table 1.

FDA's current regulatory framework permits and encourages new alternative methods to animal testing, as described in various Agency regulations and guidance documents. FDA encourages sponsors to consult with the Agency through the Q-Submission process if they wish to use a non-animal testing method suitable, adequate, validated, and feasible for the intended regulatory endpoint. FDA supports alternative methods backed by science that produce scientifically valid data appropriate within a context of use to meet the regulatory needs of one of FDA's centers. As FDA and the scientific community continue to implement the 3Rs, it is important to recognize that considerably more research and development is needed for tools that might replace, reduce, or refine the large battery of animal studies that currently support a multitude of toxicity, safety, and effectiveness assessments.

FDA has multiple working groups to support advancing alternative methods and that reduce animal testing. These working groups are informational; they do not offer formal regulatory or product guidance.

The FDA Alternative Methods Working Group, established in 2019 to further the goals of the FDA Predictive Toxicology Roadmap, is composed of senior reviewers and researchers from all Centers and the Office of Regulatory Affairs (ORA). It focuses on opportunities for evolving innovative technologies and new areas of science that support alternative methods extending across FDA's product and regulatory areas.

Modeling and Simulation Working Group: Computational modeling and simulation tools complement traditional methods for gathering evidence about FDA-regulated products or developing FDA policy across Centers. Key objectives include: 1) Raising awareness about modeling and simulation to advance regulatory science; 2) Fostering enhanced communication about modeling and simulation efforts among stakeholders; 3) Serving as a scientific resource on modeling and simulation and emerging technologies for FDA; 4) Collaborating with national and international organizations pursuing similar activities; and 5) Promoting consistent review and decision-making with modeling and simulation across FDA.

FDA Toxicology Working Group, published the FDA Predictive Toxicology Roadmap in 2017, describing FDA's thoughts on viable ways to foster the development and evaluation of emerging toxicological methods and new technologies to incorporate them into FDA regulatory review. This working group, which includes senior toxicologists across FDA's Centers and Offices, has also held public events, including a public hearing in 2018 and a public workshop in 2019.

Table 1: Examples of FDA Efforts to Advance Alternative Methods

Activity	Description
Human organ chips for radiation countermeasure development	In this FDA-funded project, scientists develop models of radiation damage in lung, gut, and bone marrow organs-on-chips and use these models to test medical countermeasures to treat such damage. This study was expanded to add development and evaluation of new organs-on-chips to aid development of countermeasures for COVID-19.
CFSAN's Work on Organ-Chip Technology	Beginning with a liver-chip, scientists in FDA's Center for Food Safety and Applied Nutrition (CFSAN) evaluate the effectiveness of this technology to better understand the effects of chemicals in food on the human body.
Strengthening coronavirus models with systems biology and machine learning	The scientific community currently uses several methods to evaluate nonclinical models in support of COVID-19 medical countermeasure development, including virus replication, histopathology, immunology data read-outs, and observation of clinical signs. The research performed during this project will help refine the methods to assess existing nonclinical models for SARS-CoV-2 and develop new models using novel approaches and technologies, which will ultimately support development and evaluation of medical countermeasures against COVID-19 as well pathogens that may emerge with pandemic potential.
Three-Dimensional (3D) Cell Culture (Microphysiological)	CDER researchers are investigating NAMs, including microphysiological (MPS) platforms, that provide additional and sometimes more focused safety information, to expand on the *in vivo* data submitted by drug sponsors in

Platforms as Drug Development Tools	regulatory applications. Some of these platforms recreate 3D physiological settings *in vitro* that may enhance the understanding of both drug pharmacology and toxicology. Also see: Impact Story: Evaluating the Potential of Microengineered Human Cellular Systems to Predict Drug Effects in the Clinic
CDRH's work on virtual population (ViP) models	A set of detailed high-resolution anatomical models created from magnetic resonance image (MRI) data of volunteers. Since their inception, the ViP models have become the gold standard for *in silico* biophysical modeling applications. Over 600 premarket applications at CDRH have cited and used the models.
Expanding next-generation sequencing tools to support pandemic preparedness and response	FDA-ARGOS database updates may help researchers rapidly validate diagnostic tests and use qualified genetic sequences to support future product development. Researchers can use the FDA-ARGOS database—a validated source of reference datasets—along with bioinformatics tools to validate the performance, sensitivity, and specificity of diagnostic tests with computer modeling (*in silico*).
Cross-Species Immune System Reference	In this FDA-funded project, researchers collected data on human and animal immune responses and used the data to create species-specific immune function maps. They overlaid the maps to highlight differences and similarities and mapped immune responses to certain biothreat agents and possible medical countermeasures in humans and animal models.
Alternative Methods for Evaluating Locally Acting, Non-systemically Absorbed Drugs in Canine Disintegrating or Chewable, Single Layer Combination Drug Products	This non-terminal research study is designed to gather data needed to support reducing or eliminating the use of dogs in certain studies that lead to the approval of medicines used to treat certain illnesses in dogs. The dogs involved in this study were retired for adoption into pet homes at the conclusion of the study.
Centers of Excellence in Regulatory Science and Innovation (CERSI) Project	Leveraging Human Brain Organoids for Mixture Neurotoxicity and the Understanding of Individual Susceptibilities External Link Disclaimer
Ongoing research and publication	List of Publications Co-authored by FDA on Alternative Methods
National Center for Toxicological Research (NCTR) projects highlighted in NCTR 2022 Annual report	• Evaluating the developmental neurotoxicity of inorganic arsenic exposure in zebrafish for regulatory risk assessment • Evaluation of drug toxicity on placenta immunity using a microphysiological human placental barrier model • Advance microphysiological system-based study of Zika virus infection in testes, viral transmission and antiviral countermeasures • Evaluation of new alternative models of folliculogenesis for assessing drug/chemical toxicity • Integrating pharmacokinetics and adverse effects data from the agency approval documents with the rule-of-two model to improve the assessment of hepatotoxicity risk • Development of an artificially intelligent virtual pregnant woman modeling suite to support regulatory decisions • Performance of 3D-bioprinted human skin equivalents for in vitro dermal absorption testing of FDA-regulated drugs and cosmetic ingredients used for dermal and transdermal applications • Establishment of a liver-chip system to predict individual susceptibility and adaptation to drug-induced liver injury • Examining ethnic and racial disparities in critical care delivery to heart failure patients with artificial intelligence and real-world data • Comprehensive evaluation of drug-induced cardiotoxicity with induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) • Development of artificial intelligence methods for food safety

3. Recommendations and Rationale

Recommendation #1: Create a Central NAMs Office to Assure Central Communication Focus and Drive Effective Partnerships

Create a central NAMs office that can provide an agency-wide strategy to coordinate and drive effective and efficient prioritization and implementation (execution) of NAMs. This will "signal" to critical stakeholders and partners that FDA is committed and serious about driving change with the adoption of NAMs, as appropriate. This will include assuring an impactful communication focus and driving effective partnerships.

Addresses FDA Charge Questions:

- FDA is interested to spur the adoption of scientifically valid alternative methods for regulatory use. What factors should FDA consider in pursuing this goal? What measures are necessary to ensure confidence in these data? What steps are necessary to ensure adoption of these new alternative methods?
- FDA has provided information on its website stemming from Agency-wide scientific working groups, for example: FDA's Predictive Toxicology Roadmap by FDA's Toxicology Working Group and Advancing Alternative Methods Report by FDA's Alternative Methods Working Group. What mechanisms can best communicate FDA's continued progress on this topic?
- FDA regularly engages the external scientific community to advance the Agency's public health mission. What additional types of collaborations and partnerships, across national and international industry, academia, and government partners should FDA pursue to facilitate adoption of scientifically valid alternative methods in regulatory context of use? Are there recommended strategies for prioritizing and coordinating such collaborations and partnerships? For international regulatory counterparts, are there additional opportunities for information sharing?

Introduction

Fostering the adoption of new technologies that will **r**educe, **r**efine, and/or **r**eplace (the "3Rs") the use of animals in the safety assessment of products are important broadly for the FDA. Various molecular, cellular, biochemical, and computational technologies are maturing rapidly, requiring a new vision and structure to ensure rapid and effective implementation of these NAM technologies. Since these approaches have the potential to make new product evaluation more efficient and effective, possibly more cost effective in the long run, and more bioethical by decreasing or minimizing the use of animals, it is in the best interest of public health to expedite implementation as an agency-wide initiative.

It is a critical time; while FDA staff and experts have gained expertise with these new platforms for regulatory decisions, the present "grass roots," loosely-coordinated approach, misses an opportunity to capitalize on all collaborative synergies to advance rapidly. The common scientific approaches, tools, and platforms used across the agency makes an emergent synergy possible. The creation of common knowledge, strategy, advocacy, funding and a center of review and prioritization, a "center of excellence," could create tremendous value. Several interdependent

changes and initiatives, outlined in these recommendations will be needed to drive this paradigm shift. This recommendation will focus on the central office, communication, and collaboration.

Specific Justification for Creation of Central Coordination Office

- While there has been significant activity identifying qualification approaches, there **has been very modest success in adoption of new NAMs into regulatory framework**; this reality may indeed be due to technological immaturity, but it appears that other contributors may include organizational barriers. Partly driven by limited resources, FDA has taken a decentralized, localized approach to the design and implementation of NAMs. This means that local initiatives have evolved at the divisional level (Table 1, Appendix) with self-organizing, cross-divisional, and extramural collaborative qualification initiatives.

- While there have been some successes in qualification and implementation, overall, there is **significant heterogeneity** in both depth and breadth of approach. While different approaches based on divisional needs are required, local development can cause confusion, overlap, and redundancy. FDA-wide guidance documents and process for continuous and coordinated learning through the agency will be needed.

- **Different implementation processes** can also cause confusion across the agency and creates the potential for internal conflict, coordination challenges, and importantly, barriers to organizational execution and excellence. Thus, there are limits to a decentralized approach. While self-organization during early adoption had benefits, it does not allow for efficiencies of scale, speed and power of a central voice. It is critical for FDA to be seen as pursuing these new approaches aggressively.

- The implementation of **NAMs and 3Rs alternatives for use in regulatory decisions is different from the development of new technologies for product-specific therapeutics**; in essence, this approach is a paradigm shift for regulatory decision-making where new technologies may make regulatory review processes more efficient, effective, and have implications outside of the agency. Centrally-driven development and coordination will strengthen FDA influence among public, private, and global partnerships (while encouraging private and other ex-FDA developers of these technologies).

Therefore, the subcommittee believes that the key enabler to facilitate the NAMs initiative across the FDA is a central coordinating office with knowledgeable leadership. This approach can efficiently champion, drive, and manage the implementation, trade-offs, priorities, processes, resources, central quality control, and best practices, leveraging a wide scientific and global community, while allowing for specific, FDA product center divisional optimization (Figure 1).

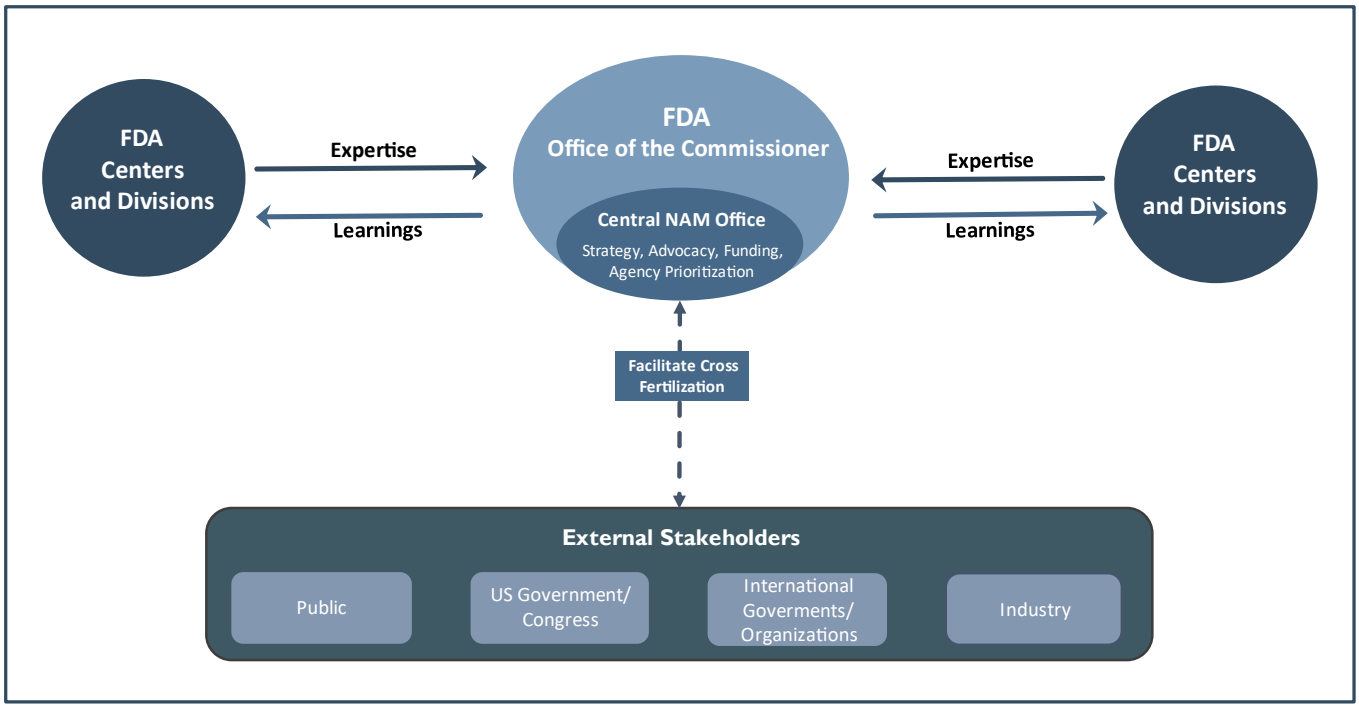

Figure 1: *Proposed Central Office Structure Showing Responsibilities and Relationships*

Implications of Creating a Central Office

- **Develop a central office road map:** It is recommended that the FDA develop a central vision, a roadmap, to drive coordinated NAMs implementation. This roadmap should include processes that allow for individual product center needs but reach back to one set of centralized, core guiding principles. For example, the agency will need to make trade-offs and focus on priority scientific/technical areas where quick wins can be achieved. This approach will foster momentum and establish a culture for this change across the agency.
- **Organization:** It is recommended that a single NAMs coordinator, along with a committee of senior staffers from each Center and NCTR, be appointed within the Office of the Commissioner to oversee the overall NAMs program at FDA.
- **Prioritization:** Commensurate with the degree of funding, this committee would be responsible for developing a continually updated, cross-agency prioritized list of areas for NAMs development. This office will also be able to manage scarce resources to maximum effectiveness.
- **Facilitate implementation, let others develop:** FDA should focus on being the central facilitator and not primary developer of these new technologies (while leveraging intramural research to grow expertise). FDA could gain most value by providing incentives, to advocate for and facilitate the development of NAMs and 3Rs alternatives by external parties through provision of clear statements about FDA's biggest needs/objectives. Likewise, FDA needs to develop proactive and growing awareness among key stakeholders: other governmental and non-governmental agencies and industry, to help develop these new technologies and partner with FDA on policy development. Shifting to a managing/driving implementation role will require FDA to be effective and more aggressive in its engagement in global, cross-sector partnerships.

- **Champion implementation:** This centralized function must drive the process to achieve agency-wide success. A centralized office drives effective external communication and promotes best practices. These include effective advocacy with key stakeholders, funders, and developers, effective and goal-directed communication both internally and externally.
- **Advocacy within and outside FDA:** Critically, there has been lack of a strong, centralized voice for funding needs despite calls to action from Congress and outside interest groups. An integrated voice to legislators, the public and interest groups will be a key role for a central office.

Communication

The development of a central communication infrastructure is critical to fill current gaps.

The need to establish a cohesive and centralized communication strategy around goals, a roadmap, and achievements in the application of NAMs toward FDA product decisions, is critical. The central communication focus should involve high-level FDA officials, including the Commissioner and Chief Scientist, to regularly address this priority through public statements, press releases, and stakeholder engagements.

Current Status Regarding Communication

- **Lack of Centralized Communication across FDA**: FDA's communication efforts regarding NAMs are currently fragmented and inconsistent. Information is disseminated through local channels without a unified strategy regarding FDA's stance and progress in adopting NAMs.
- **Limited Awareness**: Many internal and external stakeholders, including legislators, researchers, government funding agencies, sponsors, FDA reviewers, and the lay public, are not fully aware of the FDA's efforts and achievements. The current communication methods do not effectively reach all interested parties.
- **Inconsistent Messaging**: There is no standardized messaging or central platform where stakeholders can access comprehensive information about FDA's NAMs initiatives.

Rationale for the Recommendation: Promotes Proactive Approach

- **Driving Adoption of NAMs**: A centralized communication focus will enable FDA to actively promote NAMs adoption. Highlighting the benefits of NAMs will encourage stakeholders.
- **Clarifying Definitions**: Clear and consistent communication can help define and explain key concepts, including how each of the key principles within the 3Rs framework can reduce animal usage and enhance the FDA mission. This will help manage stakeholder understanding of limitations and future possibilities of NAMs, while managing expectations.

Enhances Transparency and Trust

- **Building Trust with Stakeholders**: Regular and transparent communication about FDA's NAMs initiatives will build trust, demonstrating the agency's commitment to innovation and ethical practices. Transparency will also showcase the FDA's dedication to developing and adopting novel innovative approaches in its mission to protect public health.
- **Addressing Concerns**: By proactively and openly addressing progress and challenges, FDA can manage expectations and mitigate potential concerns or misunderstandings, fostering a collaborative environment.

Facilitates Coordination and Efficiency

- **Central Coordination**: A centralized communication strategy will streamline efforts across different divisions, ensuring that all parts of FDA are aligned and working towards the same goals. In addition, this fosters a learning environment.
- **Effective Message Cascades**: Developing message cascades will ensure that key messages are consistently and uniformly communicated from a centralized office to all relevant stakeholders, including legislators, researchers, government funding agencies, developers, FDA reviewers, and the public.

Importance of Communication to Specific Stakeholders

- **Sponsors and Industry Leaders**: Clear communication is crucial for sponsors and industry leaders to understand the regulatory landscape and the FDA's expectations, encouraging alignment.
- **Government Funding Agencies**: Effective communication with government funding agencies (e.g., National Institutes of Health [NIH], BARDA, DARPA, ARPA-H) highlighting FDA's commitment and progress can help secure necessary funding for research and development.
- **Congress**: Regular updates to Congress about the FDA's progress in NAMs adoption can ensure continued legislative support and funding. It can also help in shaping policies that facilitate the adoption of NAMs.
- **Public**: Public understanding and support are crucial for acceptance and implementation. Educating the public about the benefits of NAMs can build broader support where there is already considerable interest.
- **FDA Reviewers**: Providing FDA reviewers with clear, consistent information and training on NAMs will ensure more efficient and effective regulatory reviews.

Desired State for FDA's Communication Strategy

- **Centralized Communication Hub**: Establish a single, user-friendly communication hub that houses all relevant information about FDA's NAMs activities. This hub should be easily accessible via FDA's website and provide information for different stakeholder groups.
- **Proactive and Consistent Messaging**: Develop and disseminate integrated, consistent messages that clearly articulate FDA's goals, progress, and challenges related to NAMs.
- **High-Level Engagement**: Ensure that top FDA officials, including the Commissioner and Chief Scientist, are actively promoting the agency's work on NAMs through speeches, interviews, and public appearances. Their involvement will lend credibility and importance to the initiative.

Other Specific Mechanisms for Effective Communication

- **Create key messages and an easily accessible communication page** to promote the agency's proactive approach to NAMs adoption.
- **Highlight that the interest in NAMs is not just to replace animal testing but also to reduce and refine current methodologies**. This includes clarification of the 3Rs framework to manage expectations about what NAMs can currently achieve in the near-term and in the future.

- **Enable central coordination of key messages and develop message cascades** that communicate FDA's strategic plan and goals to all stakeholders, including legislators.

Key Foundational Documents to Highlight

- **FDA's Predictive Toxicology Roadmap**: This roadmap by FDA's Toxicology Working Group provides a comprehensive guide on predictive toxicology methods and their regulatory applications.
- **Advancing Alternative Methods Report**: This report by FDA's Alternative Methods Working Group outlines the progress and future direction of alternative methods in regulatory science.

Additional Mechanisms to Explore

- **Interactive Webinars and Virtual Town Halls**: Interactive webinars and virtual town halls can provide stakeholders with real-time updates and allow for direct engagement.
- **Dedicated NAMs Newsletter**: A periodic and/or targeted newsletter focused exclusively on NAMs can keep stakeholders informed about recent developments, upcoming events, and significant milestones.
- **Social Media Campaigns**: Utilizing social media platforms to share updates, infographics, and short videos about NAMs can reach a broader audience and foster greater public engagement.
- **Stakeholder Workshops and Conferences**: Organizing workshops and conferences to discuss progress and the future for NAMs fosters collaboration and feedback.
- **Enhanced Website Features**: Improving the FDA's website to include a dedicated section for NAMs would be useful as an interface with key stakeholders.

Mechanisms to Communicate Continued Progress

- **Annual Progress Reports**: Publishing detailed annual reports that summarize the FDA's progress, challenges, and future regarding NAMs will provide transparency.
- **Press Releases and Media Briefings**: Issuing regular press releases and conducting media briefings to announce significant milestones, new initiatives, and collaborative efforts.
- **Collaboration with Scientific Journals**: This will ensure that the scientific community is well-informed about the latest developments.
- **Community Engagement Programs**: Through local events, school programs, and partnerships with community organizations.
- **Interactive Online Platforms**: Where stakeholders can ask questions, provide feedback, and access educational resources.

Collaboration

Collaboration should focus on creating efficiency and synergy within FDA and, importantly, on external partnerships.

While collaboration efforts within FDA have been well documented to the committee, these efforts appear to lack efficiency, synergy, and impact. By creating a centralized NAMs office to coordinate such efforts, FDA will be able to foster collaboration, promote interdependencies while streamlining processes, avoiding duplication of efforts, and ensuring consistency and transparency.

In this context, limiting collaborations, partnerships and other interactions solely within FDA is deemed inappropriate. It is the subcommittee's opinion that external partnerships must be rigorously pursued to accelerate the implementation of new technologies, practices, and regulations within FDA. There are hosts of international and national regulatory agencies, academic researchers, patient advocacy groups, and industry experts engaged in the development of NAMs for regulatory purposes. Collaborating with these external stakeholders across these employment platforms will allow FDA to widen and diversify its perspectives, expertise, and reach. FDA is not fully versed (as most technology developers sit outside FDA) with state-of-the-art NAMs technologies; as such, these partnerships will ensure FDA is better informed about the latest developments and can gain access to specialized knowledge or capabilities.

By partnering with external stakeholders, FDA will:

- Help build credibility and transparency.
- Increase accountability and enhance the efficacy of regulatory processes.
- Facilitate knowledge exchange, capacity building, and enable and encourage continuous internal improvements.
- Establish best practices and continuous learning to ensure staff is aware of the latest developments.

The proposed central NAMs office should collaborate with similar groups in other agencies or institutes within the US (e.g., EPA, ICCVAM) and in other countries (e.g., JRC, ICH, other regulatory bodies) as well as with industry.

A central FDA NAMs office composed cross-functionally of experts from all FDA centers (e.g., regulatory, scientific, legal, communication) can provide the core team to harmonize initiatives with international regulatory agencies to permit alignment of standards, streamlining of regulatory processes, and facilitating the global adoption of regulatory changes or guidelines.

In addition, the central FDA NAMs office should be charged to assure coordination of FDA's pursuit of collaborations with patient advocacy groups, industry associations, or other external stakeholders. These relationships are critical to gather feedback, input, and perspectives on regulatory decisions, allowing for increased transparency, trust building, and the promotion and adoption of new regulations or policies, including establishing "Guidance to Industry" for the rules for NAMs development.

Critically, FDA must encourage, facilitate, and incentivize organizations outside of FDA (industry and others) to be the engine of these new NAMs platforms and product-specific technologies; solely developing these technologies within FDA will not be feasible.

Efforts should include:

- Development of an infrastructure enabling these collaborations.
- Participation of industry, large and small companies, including consortia with clearly listed incentives for companies to participate.

- Participation of other stakeholder organizations and other regulatory agencies for worldwide consistency.
- Educate all partners on how to interpret NAMs data and the methods' usefulness and limitations.
- Create opportunities for regulators, developers, and end-users to collaborate early and often to facilitate NAMs development, validation, and adoption.
- Set reasonable regulatory expectations for NAMs. It is critical that NAMs demonstrate relevance to human biology by reflecting key events along adverse outcome pathways.
- Develop a framework outlining qualification requirements. This framework should be developed collaboratively, focus on the context of use, and be flexible to allow for cases when comparison to animal data is not possible or appropriate.
- Establish a robust data-sharing infrastructure, and a registry of NAMs and data that have been accepted for regulatory purposes and associated contexts of use.

For international regulatory counterparts, there are additional opportunities for information sharing:

- Establish a resource coordinating core with a searchable NAMs repository across agencies.
- Participate in major NAMs meetings and conferences, especially if organized by regulatory agencies such as JRC, ECHA or Organisation for Economic Cooperation and Development (OECD).
- Consider hosting a regular international NAMs conference involving agencies in other countries and potentially, form a coordination council to support the development and assessment of NAMs tools (OECD QSAR Toolbox effort).

Recommendation #2: Determine Effective Metrics

Determine effective metrics that can demonstrate the impact of ongoing FDA investments in NAMs (wider FDA).

Addresses FDA Charge Question:
FDA has provided information on its website stemming from Agency-wide scientific working groups, for example: FDA's Predictive Toxicology Roadmap by FDA's Toxicology Working Group and Advancing Alternative Methods Report by FDA's Alternative Methods Working Group. What other mechanisms should FDA explore to ensure its efforts are readily understood and to effectively communicate a cohesive and comprehensive strategy to advance the qualification and adoption of alternative methods for regulatory use?

Introduction

To assure effectiveness and provide a platform for facilitating adoption and future investment/prioritization decisions, FDA should, through the creation of the central office on NAMs, **assure adoption of informative metrics that can be reviewed by internal and external stakeholders on a regular basis to provide opportunities for learning and program adaptations**. FDA should establish a strategic/management plan that is linked with the central NAMs adoption roadmap to clearly illustrate the connection between these cross-agency research efforts and how they link to effectively address varying needs/priorities of different centers. Transparency on the alignment of the distribution/allocation of the likely limited resources to determined priorities will enable focus to maximize broader FDA and public impact.

In addition, since movement to alternative methods requires a more robust dialogue with technology and research stakeholders (e.g., National Institute of Health) on what testing methods are acceptable and what outcomes from the tests are desired, the transparency of metrics and FDA progress/needs will help align stakeholder research investments as well.

Rationale for Metric Creation and Adoption

Considerations for creation of metrics should be based on objectives, timelines/milestones, and means to measure impacts. Impact should be considered from the view of a variety of stakeholders and consider technical, financial, and political factors. However, above all else, they should be directly aligned with the primary FDA mission and should demonstrate the progress towards the aspiration for NAMs to help develop effective and safe products in the fastest way possible.

Suggested Metrics for Implementation
Central tracking of all cases where NAMs/3Rs alternatives were included in a regulatory submission/product review and played a role in an individual product decision approval or removal from market (for weight of evidence, waiver, urgent decision for emergency or breakthrough use, etc.). Case tracking should include the product center, and the regulatory decision, and the alternative method involved. Since it is likely that product reviewers will need to enter these data, the entry should be easy and not overly burdensome.

This should allow integration with existing metrics that centrally track the number of newly approved products per year, time to approval, and post-marketing recalls to collectively determine impact of FDA regulatory science advancement of the integration of NAMs into decisions. This should also demonstrate effectiveness for the adoption and validation by providing supportive evidence that use of NAMs assures FDA meet its foundational objective for a high standard for safety and efficacy (should assure that adoption doesn't lead to more adverse events, product recalls, etc.).

Once specific NAMs or alternative approaches are deemed accepted by the agency, then specific tracking on their use should be included in the above tracking. For example, in today's drug regulatory guidance documents, there are opportunities for sponsors to seek waivers for alternate approaches, such as for reproductive toxicology (ICH S5) and carcinogenicity studies (ICH S2), but it is not clear if the agency has kept metrics on how often this approach is pursued. For the cases in which it is pursued, is it accepted? If not accepted, what were the reasons? Tracking and transparency for such activities can help with both intra-agency and public/global learning, improvement and adoption.

Tracking of the number of animals used for a product authorization should be indexed. This would support and provide data for FDA agency initiatives related to the 3Rs. This could be a tedious exercise, but it may be possible to more easily discern this by deployment of a central artificial intelligence approach across electronic submissions. This could reveal where the biggest opportunity for NAMs may be from an animal use perspective, with respect to individual regulatory guidances (Table 5, Appendix). Ideally, over time, the ability to see the number of animals per submission per product-type, may reduce the number of total animals per submission and inform NAMs and 3Rs impact, or reveal areas that need more priority.

To determine metrics for evaluating how the use of NAMs correlates with animal usage in FDA IND submissions, the following strategies can be implemented:

Data Collection and Reporting Framework:

- **Enhanced Submission Forms**: Incorporating specific fields in IND and other submission forms to capture data on the use of NAMs alongside traditional animal models.
- **Electronic Tracking**: Utilizing electronic submission systems like Standard for Exchange of Nonclinical Data (SEND) to facilitate the tracking and analysis of NAMs usage.

Detailed Metrics on NAMs and Animal Usage:

- **NAMs Adoption Rate**: Tracking the rate at which NAMs are adopted in preclinical studies compared to traditional animal models.
- **Species and Number of Animals**: Reporting changes in the species and number of animals used when NAMs are employed.
- **Study Type and Purpose**: Categorizing studies by type (e.g., safety, efficacy, pharmacokinetics) and comparing the extent of NAMs usage in each category.

Correlation Analysis:

- **Comparative Analysis**: Analyzing correlations between NAMs usage and reductions in animal usage, including statistical comparisons.

- **Outcome Metrics**: Evaluating the outcomes of studies using NAMs versus those using traditional animal models to assess effectiveness and reliability.

Transparency and Accessibility:

- **Public Databases**: Creating and maintaining public databases or dashboards where data on NAMs and animal usage in INDs is regularly updated and accessible.
- **Annual Reports**: Publishing annual reports summarizing the data on NAMs and animal usage, including trends and correlations.

Compliance and Monitoring:

- **Audits and Inspections**: Conducting routine audits and inspections to ensure accurate reporting of NAMs and animal usage.
- **Feedback Mechanism**: Implementing a feedback mechanism for sponsors to provide comments and suggestions for improving NAMs usage reporting.

Collaboration with Stakeholders:

- **Engaging with Industry and Academia**: Collaborating with pharmaceutical companies, research institutions, and other stakeholders to develop and refine metrics and reporting requirements for NAMs usage.
- **Workshops and Conferences**: Organizing workshops and conferences to discuss best practices and challenges in implementing NAMs.

Advanced Analytical Tools:

- **Data Analytics and Visualization**: Employing advanced data analytics and visualization tools to analyze trends and patterns in NAMs and animal usage data.
- **Predictive Modeling**: Using predictive modeling to forecast the impact of NAMs adoption on future animal usage and identify potential areas for further reduction and refinement.

By implementing these strategies, FDA can effectively evaluate how the use of NAMs correlates with animal usage in IND submissions, providing valuable insights into the effectiveness and adoption of alternative models in drug development.

Assessment of FDA community and stakeholder readiness. Since some of the tools for NAMs and alternatives are not generally understood, FDA should be assessing the overall engagement and readiness for key stakeholders to adopt. This will help inform where FDA should focus efforts on central communication, workshops, etc. A consistent survey that is deployed within FDA and externally among stakeholders should provide a regular update on readiness and alignment/potential misalignment.

Additional metrics to be considered may be a bit more challenging to glean but are worth consideration. These include speed for product testing with NAMs relative to alternate test, variability, reproducibility, and confidence in results, cost for developers, cost for users, speed for product reviewers to come to a decision, etc.

Recommendation #3: Create a Framework for Qualification

Create a uniform FDA framework for qualification of NAMs

Addresses FDA Charge Question:
In addition to charge question listed under recommendation #1, FDA has product development tool qualification programs, both existing (i.e., drugs/biologics and medical devices) and under development, that can facilitate qualification of alternative methods. How can we further clarify and/or enhance existing programs and inform developing programs to help ensure submission of high-quality alternative methods data for regulatory contexts of use?

Introduction

Ideally, **development of a single FDA validation/qualification (V/Q) model** (e.g., "checklist") that is flexible and can be customized for each FDA division will enable creation of maximal value for each set of technology developed (multi-purpose). This will likely need to be a tiered framework for tests that are general and can go across multiple purposes/products. Standardization and structure of the way that "context of use" is described will inherently reflect flexibility for the range of applications.

The data "checklist" should adhere to FAIR Data Principles: **F**indability, **A**ccessibility, **I**nteroperability, and **R**eusability (Wilkinson, M. 2016). These principles apply not only to "data," but also to the algorithms, tools, and workflows that lead to that data to ensure transparency, reproducibility, and reusability. An FDA NAMs central office should review and then consider adoption of best recommendations for a "one-FDA" framework hybridized from the best features of existing examples such as Regulatory Science Tools (RST), MDDT, and iSTAND (Table 2).

As the tools are developed and brought forward, the consolidation of current protocols for method/tool development and approval across the entire constituency of FDA offices and respective products will create a powerful catalog inventory with standards that facilitate their use.

Table 2: Current qualification programs for the use of alternative methods

Program	Additional Details
FDA Center for Drug Evaluation and Research (CDER) / Center for Biologics Evaluation and Research (CBER) Drug Development Tool (DDT) Qualification Programs	• Animal model qualification program • Biomarker Qualification • Clinical Outcome Assessment Qualification • Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program - Designed to expand drug development tool types, examples include, microphysiological systems to assess safety or efficacy questions, development of novel nonclinical pharmacology/toxicology assays
FDA Medical Device (CDRH) Medical Device Development Tools (MDDT)	• Clinical Outcome Assessment • Biomarker Test • Nonclinical Assessment Model: A nonclinical test model or method that measures or predicts device function or in vivo device performance. Examples include tools that can reduce or replace animal testing or reduce test duration or sample size.
FDA Center for Devices and Radiological Health (CDRH)	CHemical RISk Calculator (CHRIS) - Color Additives tool

A recent (2023) National Academies of Sciences, Engineering, and Medicine (NASEM) report for the EPA reviewed many published approaches for scientific confidence of NAMs (see Appendix D in https://nap.nationalacademies.org/read/26906/chapter/11), and came up with the following common themes which may be useful for developing a "uniform framework" for NAMs (https://nap.nationalacademies.org/read/26906/chapter/7#84).

The key components of a scientific confidence framework for NAMs, adapted from NASEM (2023), include the following:

Intended purpose and context of use relates to the specific biological question the NAM is addressing and the situation in which the NAM may be used.

The purpose of a NAM can be commonly framed as a **p**opulation, **i**ntervention/**e**xposure, **c**omparator, and **o**utcome (PI/ECO) statement. Because NAMs are preclinical tools, they both have their own "test system" PI/ECO as well as a "target human" PI/ECO. The "test system" PI/ECO specifies the PI/ECO that is tested (e.g., P could be a cell line, or a primary cell). The "target human" PI/ECO specifies what the NAM is supposed to address in humans (e.g., P could be females of reproductive age). The use of such "parallel" PI/ECO statements enables one to succinctly catalog in a structured manner both the technological aspects of the NAM (the "test system" PI/ECO) as well as the "intended purpose" of the NAM (the "target human" PI/ECO). It would also facilitate cross-fertilization across FDA centers and regulatory needs.

The context of use of a NAM refers to how the data/outputs would be used in regulatory decision-making. For instance, the context of use may determine the degree of uncertainty (precision) that is considered acceptable. When there is no alternative, then there may be a greater tolerance for imprecision in a NAM. In another example, in the context of prioritization or screening (e.g., for tiered testing), there may be a greater tolerance for false positives compared to false negatives.

Internal validity relates to the extent of systematic error (bias) in the NAM. There is both a prospective and retrospective aspect to internal validity. Prospectively, the NAM should specify the experimental and/or computational procedures necessary to minimize bias. For example, edge-effects in in vitro assays are a known source of potential bias, and either experimental (e.g., only having media in edge wells) or computational (e.g., statistical adjustments) approaches should be specified to minimize systematic errors. Retrospectively, this information would be used to evaluate the quality of the data generated using the NAM.

External validity refers to the extent to which results from a NAM accurately represents its "target human" PI/ECO. In cases where there is human clinical data (e.g., drugs), this may be more straight-forward to establish, as compared to cases where human data are either observational or non-existent (many non-pharmaceutical chemicals). NASEM identified several sub-topics within external validity as follows:

1. Biological considerations: Population—How strong is the biological basis for the NAM as a biologically relevant model for the human population?
2. Biological considerations: Outcome—How strong is the biological basis for the NAM outcome as a model for human outcomes measured?
3. Intervention/Exposure considerations: How accurately does exposure in the NAM model human interventions/exposures?
4. Concordance: How accurately does the NAM predict human outcomes to interventions/exposure?

Biological and experimental variability: Biological variability is defined as the true differences in attributes due to heterogeneity or diversity. Therefore, biological variability cannot be eliminated but can be better characterized or controlled via rigorous experimental design. For instance, use of primary cells would introduce more biological variability across different laboratories, which could be ameliorated by using either pooled samples (e.g., for hepatocyte clearance assays) or by using larger populations (multiple donors) from which a population central tendency could be derived. Experimental variability encompasses inter- and intra-laboratory variability, repeatability, and all aspects of reproducibility. These considerations include those typically addressed in traditional "validation" protocols, such as ring trials.

Transparency refers to there being adequate information available to fully evaluate (1)–(4). Additionally, FAIR principles could be considered under this category.

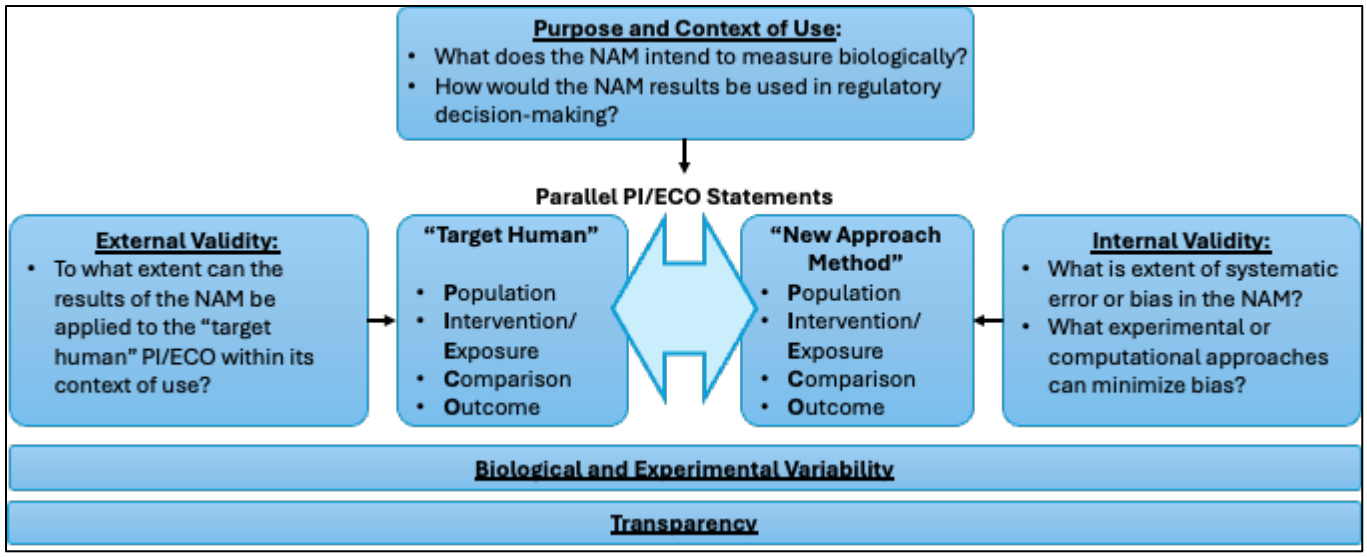

***Figure 2**: Adapted from National Academies of Sciences, Engineering, and Medicine. 2023. Building Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests. Washington, DC: The National Academies Press.*
https://doi.org/10.17226/26906

Recommendation #4: Establish Transparent and Scientifically Rigorous Review Process

Establish a transparent and scientifically rigorous review process for incoming product applications that rely on NAMs to demonstrate efficacy and/or safety

Addresses FDA Charge Question:
FDA is interested to spur the adoption of scientifically valid alternative methods for regulatory use. What factors should FDA consider in pursuing this goal?

Introduction

This recommendation **focuses on assuring FDA review staff are best prepared to embrace data from NAMs into their regulatory decisions**. NAMs are new and emerging regulatory tools, and each may have a different level of acceptance regarding "fitness" to use for regulatory decisions by FDA centers and reviewers. Therefore, to assure that "front-line" FDA product reviewers and decision-makers are prepared to leverage, FDA will need to include focus on this staff group to assure their readiness to incorporate standards and understanding into overall regulatory decision-making. FDA should coordinate a plan to develop rigorous reviewer expertise and supporting guidance to enable appropriate consideration of regulatory submissions that rely on NAMs.

The ultimate objective of this recommendation is to **assure partnership of reviewers and researchers in FDA centers as well as external stakeholders to co-develop protocols for reviewing NAMs**. We provide recommendations that will assist FDA and stakeholders in developing alternative methods for regulatory use. This might include identifying specific safety or development areas of focus, methods for assessing credibility of specific types of alternative methods, or what to include in regulatory submissions. There are already a few examples of this:

1. S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals | FDA;
2. Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions | FDA;
3. Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry | FDA;

We offer the following specific recommendation that will help FDA to coordinate product reviewer engagement and training across all FDA product centers. It is likely that these recommendations would also produce content that helps set overall strategic priorities for FDA or tool developers:

- Define problems reviewers can't address well today in the context of their product reviews. This will inform FDA priorities for investment and partner engagement (drives specificity for most urgent needs)
- Establish FDA best practices and continuous learning in "real time" with evolving examples
- Ensure FDA reviewers understand the opportunity and future implication for NAMs and 3Rs and drive a "change management/transformational" mindset to support the cultural changes needed to enable evaluation and adoption of NAMs

- Support and educate FDA reviewers and researchers in NAMs (MPS, in silico modeling, AI/ML approaches, digital twins). Provide basis for reviewers to be able to interpret and evaluate NAMs data submitted by sponsors in support of their product approvals or other regulatory decisions.
- Enable FDA researchers to keep pace with new developments in the field and inspire internal research efforts. One approach could be internal FDA workshops on various NAMs methodologies and modalities (including speaker series from internal efforts (across divisions) and external subject matter experts (developers, academics, sponsors)).
- Create an internal database of NAMs data that are in submissions reviewed by FDA. For FDA data, develop a consistent format of NAMs data (appropriate for type of NAM). Encourage consistent format for sponsor submitted data as consistent format will enable easier and more fruitful searches (analogous to SEND for safety data).
- Communicate and make transparent examples of the use of flexible, yet within guidance, reasoning, and examples of the use of new technologies to promote learning.

Table 3: Selected Examples of U.S. and International Organizations

Accelerating the Pace of Chemical Risk Assessment (APCRA), an interagency work group convened by the EPA
Animal-free Safety assessment of chemicals: Project cluster for Implementation of novel Strategies (APSIS) including Precision Tox, the Ontox consortium, and Risk-Hunt3R (Europe)
ASTM (formerly American Society for Testing and Materials), Microphysiological Standards Working Group
Center for Alternatives to Animal Testing (CAAT), Johns Hopkins University
EPA Office of Research and Development (ORD) New Approach Methodologies (NAMs) for Developmental Neurotoxicity (DNT)
European Food Safety Authority (EFSA) Working Group on New Approach Methodologies (NAM) development for Developmental Neurotoxicity (DNT)
European Organ-On-Chip Society (EUROoCS)
International Liaison Group on Methods for Risk Assessment of Chemicals in Food (ILMERAC)
IQ Microphysiological Systems Affiliate (IQ-MPS) of the International Consortium for Innovation and Quality in Drug Development
Microphysiological Systems World Summit committee
NASEM, including Institute for Laboratory Animal Research (ILAR) and Micro-Physiological Systems for Efficacy and Safety Studies: A Workshop on Advances in Organs-On-Chip Technologies for Animals
National Center for Advancing Translational Sciences (NCATS), part of the NIH, including a Memorandum of Understanding (MOU) with NIH, FDA, and the EPA to further Tox21, a partnership between FDA, EPA, National Institute of Environmental Health Sciences (NIEHS) and NCATS to advancing the science of toxicology and toxicity testing, and its application to regulatory decision making; and an MOU to further a common interest in facilitating the development of in vitro microphysiological systems that represent major organs and tissues in the human body, for prediction of efficacy, bioavailability and toxicity
NIEHS, part of NIH, Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
National Institute of Standards and Technology (NIST), Organ-on-a-Chip/Tissue-on-a-Chip Engineering and Efficacy Standardization Working Group
Society of Toxicology (SOT), including the In Vitro and Alternative Methods Specialty Section (IVAM), and an MOU to collaborate on training that addresses new methods in toxicology and their qualification, as well as alternatives to animal testing
United States Department of Agriculture (USDA)

Recommendation #5: Prioritize Key Initiatives

Identify and invest in high impact NAMs initiatives to fully execute that will aid in regulatory decisions

Addresses FDA Charge Question:
FDA seeks input from the subcommittee that will assist stakeholders developing alternative methods for regulatory use. This might include identifying specific safety or development areas of focus, methods for assessing credibility of specific types of alternative methods, or what to include in regulatory submissions. Are there other recommendations from the subcommittee and how would the subcommittee recommend prioritizing?

Introduction

The subcommittee recognizes that the range of decision contexts within FDA is extremely broad. However, each center/program tends to focus on their own specific needs and priorities, as evidenced by the different guidance documents that provide considerations as to alternative methods. There is no overall coordinated strategy for cross-pollinating technologies/approaches and regulatory needs, and priorities appear to be identified within silos rather than across the entire agency. It is highly recommended that FDA determine, by looking across the agency, a few initiatives that can be adopted in the new framework to demonstrate the value of coordination. This coordination is the basis of our overall recommendations as laid out throughout this document.

Rationale for the Recommendation of Specific Priorities

Our advice is based on the experience within the Agency in developing previous guidance documents. As an example, the FDA guidance document on Physiologically Based Pharmacokinetic (PBPK) analyses focused only on their application to drugs, even though PBPK modeling is widely applicable across a range of FDA-regulated products, from food contaminants to cosmetics. Indeed, many (non-FDA) guidance documents on use of PBPK models for occupational and environmental health substantially preceded the current FDA document by up to a decade (U.S. EPA, 2006; WHO/IPCS, 2010; EFSA 2014). Moreover, it could be argued that without the initiative and experience from other regulatory contexts, regulatory use of PBPK modeling for drugs would not have matured nearly as quickly. Another example is the use of induced Pluripotent Stem Cell-derived cardiomyocytes for preclinical screening first developed within the pharmaceutical context through the CiPA initiative (Colatsky, T. 2016).

However, even though there is a potential to fill a large data gap for other FDA-regulated products, including food additives/contaminants, tobacco products, or cosmetic ingredients, there has been little uptake in those areas. Overall, it is **likely that the Agency needs to look across diverse application areas to identify the regulatory contexts for which they are most ready for implementation with high likelihood of success and impact.** Learnings from these selected applications will be essential for broadening the application of NAMs across multiple areas.

An important priority area in which some NAMs may be impactful and successful would be products for which FDA has no pre-approval authority such as food or cosmetics (Table 4,

Appendix). Thus, in these cases, there is no required pre-clinical testing, so NAMs would be filling a data gap and support a tiered approach for testing. Suggestions for priority areas to consider include:

Food contaminants represent one area of applications for NAMs to fill data gaps, especially for data-poor substances.

- For instance, PFAS in food and food packaging can be an example where NAMs could inform regulatory decision-making where it is challenging to use traditional animal data for the many potential contaminants.
- Mycotoxins may be another good case study – since like PFAS there are hundreds of them and very few have been characterized as to their specific potential adverse health effects. In addition, interaction between mycotoxins and their combined impact on human health needs to be considered as exposure to multiple mycotoxins is expected through multiple contaminated foods consumed individually or in combination.
- This is also a complex issue because too much restriction will decrease the food supply, but too little restriction will lead to adverse effects. This is a case where "some data" is better than "no data," so the bar for using NAMs data in decision-making could be lower.

Tobacco products, particularly electronic nicotine delivery systems (ENDS), may also be an area where NAMs can fill critical data gaps. In addition to testing of individual components, NAMs (particularly medium-and high-throughput NAMs) may enable the better characterization of whole mixture effects, which may be more efficient on a product-by-product basis than the approach of examining one ingredient at a time.

Cosmetics

- Due to the ban in Europe on animal testing of cosmetic ingredients, NAMs are likely to be needed to provide data for any new **cosmetic** ingredients, as they would constitute the "best available" science. Unlike for data-poor food contaminants, in this case, these are intentionally added ingredients, so the "bar" for their use in regulatory decisions may be higher. **Pharmacokinetic-related NAMs** for cosmetic ingredients may be a "low hanging fruit," as they could be used to better characterize dermal penetration and systemic bioavailability.
- Availability of such NAMs could enable the support of testing the new paradigm of a **tiered, animal-free approach for cosmetics**. For example, a rapid, simple NAMs screen for testing the absorption of foods and cosmetics would lead to a more rigorous tier of testing for those compounds that will/will not penetrate and achieve significant concentrations throughout the body. Those that do not have potential for internal exposure could be released or assumed to not need additional in vivo testing. Alternately, this new paradigm would enable FDA to apply these NAMs tests proactively in surveillance programs or reactively after an event where consumers report adverse outcomes following use/ingestion.

Recommendation #6: Establish Central NAMs Database

Compile a central NAMs database for all of FDA to use

Addresses FDA Charge Question:
FDA is interested to spur the adoption of scientifically valid alternative methods for regulatory use. What measures are necessary to ensure confidence in these data? What steps are necessary to ensure adoption of these new alternative methods?

Introduction

There is emerging advocacy that mandatory animal testing should be revised, and alternative methods (NAMs) introduced as alternatives to animal testing in assessing product safety and efficacy. Thus, there has been substantial development of NAMs in recent years within both basic research and regulatory science (Table 6, appendix). For instance, EPA established a "New Approach Methods Work Plan" and developed NAMs training materials, and NIEHS established a NAMs Strategic Roadmap. The state of affairs is best described by the title of a recent position paper co-authored by researchers from 24 US and international organizations (including US EPA, NTP/NIEHS, and others): "New approach methodologies in human regulatory toxicology - Not if, but how and when!" (Schmeisser, S. *et al.* 2023). Thus, FDA should continue its course toward assessment of emerging NAMs developed within FDA (e.g., at NCTR) and elsewhere and develop practical approaches and protocols for adopting NAMs as part of regulatory submissions of all products withing the agency purview. It is thus recommended to establish and maintain a database of computational and experimental NAMs that have been peer-reviewed and, importantly, adopted by other regulatory agencies in the United States and elsewhere, and keep this reference database current. This program will be leveraged by a substantial body of research both within and outside of FDA. It will be important to establish protocols for consideration and transitioning of these methods from this database into FDA-approved regulatory tools that can be used by the agency reviewers when considering new products.

Rationale and Recommendations for Central Database

There is a critical challenge to establish robust protocols for approving and employing NAMs as *bona fide* regulatory assessment tools. Steps in this direction have been taken by the Agency. FDA established a NAMs program in 2023 that received internal $5M funding to: (i) Expand processes to qualify alternative methods for regulatory use; (ii) provide clear guidelines to external stakeholders developing alternative methods; and (iii) fill information gaps with applied research to advance new policy and guidance development. This program needs to be expanded to enable the Agency's transition into active use of NAMs as qualified regulatory assessment tools and these **protocols should be deposited centrally with a common framework for access**. We recommend that the new NAMs database is developed taking the following considerations into account; similar recommendations for EPA have been made by NASEM (Evaluating Scientific Confidence of NAM-Based Testing Strategies). If implemented, this database will be an excellent source for the metrics proposed in recommendation #2.

- A nascent Complement Animal Research in Experimentation (Complement-ARIE) program established by NIH in 2024 will likely provide a lot of new methods that can reduce or replace animal testing. Evidently, NIH is committed to developing NAMs. It is thus critical

that the **NAMs database consolidates respected methods and tools emerging from research programs** like Complement-ARIE.

- Target inclusion of NAMs data from other governmental agencies, e.g., NCATS, EPA, that also have significant efforts in NAMs. For instance, EPA has developed several tools that may be considered for inclusion in a new FDA NAMs database. Similarly, NIEHS/ICCVAM developed a new NAMs tool to assess skin sensitization (DASS tool).
- Explore all FDA data using modern data summarization/LLM tools. Focus on understanding historic "features" that dictated regulatory decisions (both positive and negative).
- For reviewers, develop a historical database as knowledge capture and management for future decisions and provide context. Analogous to historical in vivo databases that provide context for interpretation of new therapeutic modality and effect in animal studies. Initially develop an interrogatable internal database of results from FDA NAMs. Incorporate external non-confidential data if possible.
- Collect best practices/examples of NAMs use in specific context; include examples from outside FDA, such as other federal agencies (NIH, EPA) and international organizations.
- Catalog all current endpoints of interest to FDA where regulatory decisions (pre- or post-marketing) must be made and map existing or developing, both standard and NAMs, tools onto the landscape of regulatory needs. This will help identify gaps/focus NAMs development in tune with the most pressing Agency needs.
- Accumulate preclinical toxicological experience to help inform NAMs validation.
- Provide central registry of NAMs approaches being developed across the agency, including guide for how NAMs are described.

4. Conclusion

In conclusion, continued research and collaboration on NAMs-driven safety assessment will need to continue as part of FDA for years to come. This is best achieved by leveraging an adaptive design model which will support the ongoing evolution of new NAMs while keeping abreast of continuing technological advancements.

NAMs will need to be reliable and reproducible with strict quality control measures to minimize variability. We suggest that NAMs are best developed in a collaborative environment, with input from multiple teams and key opinion leaders with varied scientific input, advanced machine learning and data analytics tools applied across different disciplines. Qualification of specific NAMs for a matched context of use should be approved by FDA for use by its product regulators, accompanied by appropriate reviewer education and support.

Following the presentation of this report, next steps will consist of FDA determining whether any of these recommendations will be implemented to drive the integration of NAMs for future regulatory decision-making. FDA's position may be communicated at a future Science Board meeting or other venue as deemed appropriate by the Agency.

5. Appendix

Table 4: FDA Product Centers and Current 3Rs/NAMs Framework
(Source: FDA Representative Summaries to the NAM Subcommittee, March 2024)

Center	Scope of Work Examples	Existing 3Rs Framework Examples	Current Guidelines & Use of Animals (in regulatory decision-making examples)
Center for Biologics Evaluation & Research (**CBER**)	• Pre and post approval authority of products • Includes cell therapy, blood product, and vaccine approval including specialty Chemistry, Manufacturing, and Controls (CMC) • In vitro testing for safety, efficacy, potency, and safety/toxicology	• **CBER Advanced Technologies Team (CATT)**: an interactive mechanism for prospective innovators/developers of advanced manufacturing and testing technologies to discuss with CBER staff issues related to the implementation of these technologies in the development of CBER-regulated products. • I**nitial Targeted Engagement for Regulatory Advice on CBER Products (INTERACT)** Meeting: a meeting that enables sponsors to obtain preliminary informal consultation for innovative investigational products at an early stage of development on issues that are not yet at the pre-IND meeting phase. • **Advanced Manufacturing Technologies Designation Program**: A program to have interactive discussion on the early adoption of advanced manufacturing technologies that have the potential to benefit patients by improving manufacturing and supply dependability and optimizing development time of drug and biologics.	1. "Potency assurance for cellular and gene therapy products" (FDA guidance, DRAFT, December 2023) 2. Q5A(R2) Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin" (ICH guidance, January 2024)

Center	Scope of Work Examples	Existing 3Rs Framework Examples	Current Guidelines & Use of Animals (in regulatory decision-making examples)
Center for Drug Evaluation & Research **(CDER)**	• Pre and post approval authority of products • Includes Office of New Drugs, Office of Generic Drugs, Office of Surveillance and Epidemiology and others • Pharmacologic effects and mechanisms of action, attributes of drug ADME, safe "first in human" starting dose, safe maximum exploratory doses in early clinical trials, possible consequences of chronic exposure, risks for special populations (e.g., pediatrics), specific parameters to monitor more closely in clinical trials, mechanistic understanding of adverse biological change observed in animals or humans	• Office of Clinical Pharmacology **model informed drug development (MIDD)** • **Complex in vitro models (CIVMs)** • **iSTAND**	• Non-animal-based methods are routinely accepted for potency assays and encourages sponsors using animal-based potency assays to develop non-animal-based potency assays. Examples where CDER has worked to accept non-animal methods: 1. ICH S10 Photosafety Evaluation of Pharmaceuticals, 2. ICH S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals, 3. ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk, 4. ICH S1B(R1)) Addendum to S1B Testing for Carcinogenicity of Pharmaceuticals, 5. OECD Test Guideline 437 Bovine Corneal Opacity and Permeability Test Method, 6. OECD Test Guideline 439 In Vitro Skin Irritation • Developing approaches to reduce animal use (e.g., review of waiver considerations based on mechanism; use of virtual control groups to reduce number of animals needed per protocol)
Center for Devices and Radiological Health **(CDRH)**	• Pre and post approval authority of products • Regulatory Science is conducted in primarily one Office (OSEL)	• RST (tools developed and internally published in public catalog) • Develop officially qualified Medical Device Development Tools (MDDT); (voluntary, public): (i) Voluntary pathway to qualify regulatory science tools, (ii) Tools that assess safety, effectiveness or performance of a medical device, (iii) Are not intended to replace standards development and recognition or device specific guidance, (iv) CDRH intends to public ally disclose summary of evidence and basis of qualification (SEBQ) for qualified tools	• Examples of tools developed are: 1. Virtual Family, 2. MRMC, a Statistical Model Developed for use in imaging and digital pathology, 3. DRAGen for use in reducing X-ray dose for CT scanning of susceptible patients including pediatrics 4. VICTRE, the world's first fully in silico clinical trial and 5. CHRIS, used for early biocompatibility evaluation prior to design freeze

Center	Scope of Work Examples	Existing 3Rs Framework Examples	Current Guidelines & Use of Animals (in regulatory decision-making examples)
Center for Food Safety and Applied Nutrition **(CFSAN)**	• Mostly postmarket testing (17% premarket) of products • Includes: Office of Food Safety, Office of Cosmetics and Colors, Office of Nutrition and Food Labeling, Office of Dietary Supplement Program, Office of Food Additive Safety	• Evaluate new technology/approaches (focus areas are Developmental neurotoxicity, cardiotoxicity and hepatotoxicity) • 3R, in vitro and in silico methods to reduce/replace animal testing and estimate human risk • Global partnership with EFSA, ILMERAC (International Liaison Group on Methods for Risk Assessment of Chemical • Represents FDA on the Tox 21 partnership with EPA, NCATS, and NIEHS • Lead Agency representative to the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)	• CFSAN must react quickly and decisively to any potential threat to the food supply
Center for Veterinary Medicine **(CVM)**	• Pre and post approval authority of products • Human food safety (residue in production animals); microbial food safety, microbiome; In silico/in vitro models • Collaborate with CFSAN for residue in production animals (indirect food additive) • Environmental consideration	• Animal drug approval requires (i) Target animal safety, (ii) Efficacy, (iii) Human food safety (microbial food safety for production animals), and (iv) Environmental impact review	• Guidance from ICVAAM and OECD
National Center for Toxicological Research **(NCTR)**	• No product review; research support for all product review centers • Conducts comprehensive toxicological assessment of chemical/contaminant upon request of a product review center	• Quick in vitro assays for hepatotoxic, cardiotoxic, and genetic toxicology liabilities • In silico approaches to highlight structural motifs of concern, etc. • Can submit methods to be qualified per context of use to iSTAND, RST, etc.	• Not applicable

Center	Scope of Work Examples	Existing 3Rs Framework Examples	Current Guidelines & Use of Animals (in regulatory decision-making examples)
Office of Counterterrorism and Emerging Threats **(OCET)**	• Product development and risk assessment: MCM (medical countermeasure) development • Chemical and Biological Defense Program (CBDP) • Research, development, and acquisition (RDA)	• Awarded Microphysiological neuro-muscular system for botulinum neurotoxin testing (FDA/CFSAN), 2022	• Consider mechanism and context of previously approved products for use to limit testing under the "animal rule" (use alternative and modeling for risk assessment)
Office of Regulatory Affairs **(ORA)**	• Do not make guidances or approve products • Supports FDA preventative and enforcement activities	• Has been working with product centers to find alternatives and NAMs for test that use animals such as 1. mouse lethality assay (BAM 17) for confirmation of bioactive Clostridium botulinum neurotoxins in food samples once other methods have indicated presence of the neurotoxin; 2. Rabbit Pyrogen assay: an expanded analyte monocyte activation assay	• ORA may develop and validate methods or use consensus methods in the analysis of FDA products (e.g., FDA bacteriological analytical manual, FDA chemical analytical manual, US Pharmacopeia (USP), American Society for Testing and Materials, Intl. (ASTM), and International Organization for Standardization (ISO)

Table 5: Guidance Documents Related to Alternative Methods

Document Title	Status	Product(s)	Specific Disease Area
Adaptive and Other Innovative Designs for Effectiveness Studies of New Animal Drugs 268	Final	Animal Drugs	N/A
CVM GFI #116 (VICH GL23) Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Genotoxicity Testing	Final	Animal Drugs	N/A
Demonstrating Bioequivalence for Type A Medicated Articles Containing Active Pharmaceutical Ingredient(s) Considered to be Poorly Soluble in Aqueous Media, That Exhibit Little to No Systemic Bioavailability, and Are Locally Acting	Draft	Animal Drugs	N/A
General Principles for Evaluating the Human Food Safety of New Animal Drugs Used in Food-Producing Animals	Final	Animal Drugs	N/A
Use of Data from Foreign Investigational Studies to Support Effectiveness of New Animal Drugs	Final	Animal Drugs	N/A
Use of Real-World Data and RealWorld Evidence to Support Effectiveness of New Animal Drugs	Final	Animal Drugs	N/A
CVM GFI #149 (VICH GL33) Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Testing	Final	Animal Drugs, Human Foods	N/A
CVM GFI #232 (VICH GL54) - Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food- General Approach to Establish an Acute Reference Dose (ARFD)	Final	Animal Drugs; Human Food Safety	N/A
Human Gene Therapy for Hemophilia	Final	Cell and Gene Therapies (CGTs)	Hemophilia
Human Gene Therapy for Neurodegenerative Diseases	Final	Cell and Gene Therapies (CGTs)	Neurodegenerative Diseases
Human Gene Therapy for Rare Diseases	Final	Cell and Gene Therapies (CGTs)	Rare Diseases
Human Gene Therapy for Retinal Disorders	Final	Cell and Gene Therapies (CGTs)	Retinal Disorders
Potency Tests for Cellular and Gene Therapy Products	Final	Cell and Gene Therapies (CGTs)	N/A
ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin	Final	Generic Human Drugs	N/A

Document Title	Status	Product(s)	Specific Disease Area
Considerations for the Development of Chimeric Antigen Receptor CAR T Cell Products	Draft	Human Biologics	N/A
Development and Licensure of Vaccines to Prevent COVID 19 Guidance for Industry	Final	Human Biologics	COVID-19 (Antimicrobial)
ICH S6 Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals	Final	Human Biologics	N/A
Format for Traditional and Abbreviated 510(k)s	Final	Human Biologics, Medical Devices	N/A
Humanitarian Device Exemption (HDE) Program	Final	Human Biologics; Medical Devices	Rare Diseases
Biosimilars and Interchangeable Biosimilars Licensure for Fewer Than All Conditions of Use	Draft	Human Biosimilars	N/A
Scientific Considerations in Demonstrating Biosimilarity to a Reference Product Guidance for Industry	Final	Human Biosimilars	N/A
Advanced Prostate Cancer Developing Gonadotropin-Releasing Hormone Analogues	Final	Human Drugs	Prostate Cancer
Chronic Hepatitis B Virus Infection Developing Drugs for Treatment	Final	Human Drugs	Hepatitis B (Antimicrobial)
Chronic Hepatitis D Virus Infection Developing Drugs for Treatment Guidance for Industry	Draft	Human Drugs	Hepatitis D (Antimicrobial)
Clostridioides difficile Infection Developing Drugs for Treatment, Reduction of Recurrence, and Prevention	Draft	Human Drugs	C. difficile Infection (Antimicrobial)
ICH E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential -- Questions and Answers	Final	Human Drugs	N/A
ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk	Final	Human Drugs	N/A
ICH S10 Photosafety Evaluation of Pharmaceuticals	Final	Human Drugs	N/A
ICH S1C(R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals	Final	Human Drugs	
Investigational Enzyme Replacement Therapy Nonclinical Assessment	Final	Human Drugs	Inborn Errors of Metabolism
Microdose Radiopharmaceutical Diagnostic Drugs- Nonclinical Study Recommendations	Final	Human Drugs	N/A
Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route: Guidance for Industry and Review Staff	Final	Human Drugs	N/A

Document Title	Status	Product(s)	Specific Disease Area
Nonclinical Testing of Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases	Draft	Human Drugs	Severely debilitating or life-threatening (SDLT) disease caused by genetic variants
Nonclinical Testing of Orally Inhaled Nicotine-Containing Drug Products	Final	Human Drugs	Tobacco Use, Smoking Cessation
Oncology Pharmaceuticals Reproductive Toxicity Testing and Labeling Recommendations	Final	Human Drugs	Cancer
Oncology Therapeutic Radiopharmaceuticals Nonclinical Studies and Labeling Recommendations	Final	Human Drugs	Oncology
Osteoporosis Nonclinical Evaluation of Drugs Intended for Treatment Guidance for Industry	Final	Human Drugs	Osteoperosis
Physiologically Based Pharmacokinetic Analyses — Format and Content	Final	Human Drugs	N/A
Rabies Developing Monoclonal Antibody Cocktails for the Passive Immunization Component of Post-Exposure Prophylaxis	Draft	Human Drugs	Rabies (Antimicrobial)
Smallpox Variola Virus Infection Developing Drugs for Treatment or Prevention Guidance for Industry	Final	Human Drugs	Smallpox (Antimicrobial)
Testicular Toxicity Evaluation During Drug Development	Draft	Human Drugs	Testicular Toxic
Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment	Final	Human Drugs, Human Biologics	Leukemia (Blood Cell Cancer)
Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases Q A_REV 1	Draft	Human Drugs, Human Biologics	Infectious Diseases (Antimicrobial)
Bispecific Antibody Development Programs	Final	Human Drugs, Human Biologics	N/A
COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products	Final	Human Drugs, Human Biologics	COVID-19
Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products Draft Guidance for Industry	Draft	Human Drugs, Human Biologics	N/A
Development of Anti Infective Drug Products for the Pediatric Population	Final	Human Drugs, Human Biologics	Infectious Diseases (Antimicrobial)
Drug Products, Including Biological Products, that Contain Nanomaterials	Final	Human Drugs, Human Biologics	N/A

Document Title	Status	Product(s)	Specific Disease Area
General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products	Final	Human Drugs, Human Biologics	N/A
ICH M10 Bioanalytical Method Validation and Study Sample Analysis	Final	Human Drugs, Human Biologics	N/A
ICH M3(R2) - Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization	Final	Human Drugs, Human Biologics	N/A
ICH S11 Non-Clinical Safety Testing In Support of Development of Pediatric Pharmaceuticals	Final	Human Drugs, Human Biologics	N/A
ICH S12 Nonclinical Biodistribution Considerations for Gene Therapy Products	Final	Human Drugs, Human Biologics	N/A
ICH S1B(R1) Addendum to S1B Testing for Carcinogenicity of Pharmaceuticals	Final	Human Drugs, Human Biologics	N/A
ICH S3A Guidance- Note for Guidance on Toxicokinetics- The Assessment of Systemic Exposure in Toxicity Studies: Focus on Microsampling- Questions and Answers	Final	Human Drugs, Human Biologics	N/A
ICH S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals	Final	Human Drugs, Human Biologics	N/A
ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals	Final	Human Drugs, Human Biologics	Cancer
ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals--Questions and Answers	Final	Human Drugs, Human Biologics	Cancer
Male Breast Cancer Developing Drugs for Treatment	Final	Human Drugs, Human Biologics	Male Breast Cancer
Mucopolysaccharidosis Type III Sanfilippo Syndrome Developing Drugs for Treatment	Draft	Human Drugs, Human Biologics	Mucopolysaccharidosis 20 type III (MPS III; also called Sanfilippo syndrome)
Nonclinical Considerations for Mitigating Nonhuman Primate Supply Constraints due to COVID-19 Pandemic	Final	Human Drugs, Human Biologics	N/A
Nonclinical Safety Evaluation of the Immunotoxic Potential of Drugs and Biologics Guidance for Industry	Final	Human Drugs, Human Biologics	N/A

Document Title	Status	Product(s)	Specific Disease Area
Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans	Final	Human Drugs, Human Biologics	N/A
Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format	Draft	Human Drugs, Human Biologics	Pregnancy/Lactation
Product Development Under the Animal Rule	Final	Human Drugs, Human Biologics	N/A
Qualification Process for Drug Development Tools	Final	Human Drugs, Human Biologics	N/A
Rare Diseases- Early Drug Development and the Role of Pre-IND Meeting Guidance for Industry	Draft	Human Drugs, Human Biologics	Rare Diseases
Rare Diseases: Common Issues in Drug Development - Guidance for Industry	Draft	Human Drugs, Human Biologics	Rare Diseases
Setting Endotoxin Limits During Development of Investigational Oncology Drugs and Biological Products	Draft	Human Drugs, Human Biologics	Cancer
Severely Debilitating or Life-Threatening Hematologic Disorders- Nonclinical Development of Pharmaceuticals	Final	Human Drugs, Human Biologics	Hematologic Disorders
Sponsor Responsibilities Safety Reporting Requirements and Safety Assessment for IND Bioavailability-Bioequivalence Studies	Draft	Human Drugs, Human Biologics	N/A
Tissue Agnostic Drug Development in Oncology	Draft	Human Drugs, Human Biologics	Oncology
Bioanalytical Method Validation	Final	Human Drugs, Human Biologics, Animal Drugs	N/A
Pyrogen and Endotoxins Testing: Questions and Answers	Final	Human Drugs, Human Biologics, Medical Devices, Animal Drugs	N/A
Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions	Final	Medical Devices	N/A
Bone Anchors - Premarket Notification 510(k) Submissions	Final	Medical Devices	Orthopedics
Characterization of Ultrahigh Molecular Weight Polyethylene (UHMWPE) Used in Orthopedic Devices	Final	Medical Devices	Orthopedics
Class II Special Controls Guideline In Vitro Diagnostic Devices for Bacillus spp. Detection	Final	Medical Devices	Bacillus infection (Antimicrobial)

Document Title	Status	Product(s)	Specific Disease Area
Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device	Final	Medical Devices	N/A
Coronary, Peripheral, and Neurovascular Guidewires – Performance Tests and Recommended Labeling	Final	Medical Devices	Vascular disease (cardio, peripheral, neuro)
General Considerations for Animal Studies for Cardiovascular Devices **(Superceded)**	Final	Medical Devices	Cardiovascular
General Considerations for Animal Studies Intended to Evaluate Medical Devices: Guidance for Industry and FDA Staff	Final	Medical Devices	N/A
Implanted Brain-Computer Interface BCI Devices with Paralysis or Amputation	Final	Medical Devices	Brain-Computer Interface Devices
Mouse Embryo Assay for Assisted Reproduction Technology Devices	Final	Medical Devices	Assisted Reproduction (OB/GYN)
Non-Clinical and Clinical Investigation of Devices Used for the Treatment of Benign Prostatic Hyperplasia (BPH)	Final	Medical Devices	Benign Prostatic Hyperplasia (GI-Urology)
Non-Clinical and Clinical Investigation of Devices Used for the Treatment of BPH	Draft	Medical Devices	Benign Prostatic Hyperplasia (GI-Urology)
Peripheral Percutaneous Transluminal Angioplasty PTA and Specialty Catheters Premarket Notification 510(k) Submissions	Final	Medical Devices	Peripheral percutaneous transluminal angioplasty (Cardiovascular)
Peripheral Vascular Atherectomy Devices - Premarket Notification 510(k) Submissions	Final	Medical Devices	Peripheral vascular atherectomy (Cardiovascular)
Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act	Final	Medical Devices	N/A
Premarket Notification (510(k)) Submissions for Electrosurgical Devices for General Surgery	Final	Medical Devices	N/A
Procedures for Handling Post-Approval Studies Imposed by Premarket Approval Application Order	Final	Medical Devices	N/A
Qualification of Medical Device Development Tools	Draft	Medical Devices	
Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions	Final	Medical Devices	N/A
Technical Considerations for Medical Devices with Physiologic Closed-Loop Control Technology	Draft	Medical Devices	N/A
The Least Burdensome Provisions Concept and Principles	Final	Medical Devices	N/A

Document Title	Status	Product(s)	Specific Disease Area
The Special 510(k) Program	Final	Medical Devices	N/A
Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Draft	Medical Devices	N/A
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process	Final	Medical Devices	N/A
Benefit Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications 510(k) with Different Technological Characteristics	Draft	Medical Devices, Human Biologics	N/A
Biocompatibility Testing of Medical Devices – Standards Specific Information for the Accreditation Scheme for Conformity Assessment (ASCA) Pilot Program	Final	Medical Devices, Human Biologics	N/A
Breakthrough Devices Program	Final	Medical Devices, Human Biologics	N/A
Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program	Final	Medical Devices, Human Biologics	N/A
Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems - Guidance for Industry	Final	Tobacco Products	N/A

Table 6: Examples of Current/Ongoing NAMs-Related Activities

Example Activities
Advancing Alternative Methods Reports
Advancing Alternative Methods for Regulatory Use
Animal Testing & Cosmetics
Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions
FDA also accepts alternative methods from OECD guidelines for some product types: • OECD Test Guideline No. 437: Reconstructed human cornea-like epithelium model replaced rabbit tests for eye irritation for pharmaceuticals, and • OECD Test Guideline No. 439: A 3D reconstructed human epidermis model is accepted for human pharmaceuticals, when warranted, to assess primary dermal irritation.
FDA's Predictive Toxicology Roadmap
Focus Areas of Regulatory Science (FARS) report
Guidance for Industry: Pyrogen and Endotoxins Testing: Questions and Answers, 2012
How Simulation Can Transform Regulatory Pathways (FDA Grand Rounds lecture recording, August 2018)
Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations Guidance for Industry, 2019
Regulatory Science Research Tools for Medical Countermeasure Development
Catalog of Regulatory Science Tools to Help Assess New Medical Devices
What are medical countermeasures?

6. Additional References

Colatsky T, *et al., Journal of Pharmacological Toxicological Methods*. **81**, 2016

European Commission: Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs and Cronin, M., *Report of the European Commission workshop on "The Roadmap Towards Phasing Out Animal Testing for Chemical Safety Assessments" – Brussels, 11-12 December 2023*, Publications Office of the European Union, 2024, *https://data.europa.eu/doi/10.2873/34576*

Golden, E. *et al., ALTEX*. **41**, 2024

National Academies of Sciences, Engineering, and Medicine. 2023. Building Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests. Washington, DC: The National Academies Press. https://doi.org/10.17226/26906

Schmeisser, S. *et al. Environ. Intl.* **178**:2023

Stucki, A. O. *et al.*, *Front. Toxicol.* **4**, 2022

Wilkinson, M. *et al. Sci Data* **3**, 2016