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Federation of American Societies for Experimental Biology

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Advisory Committee to the Director
Working Group on Catalyzing the Development and Use of Novel Alternative Methods to Advance Biomedical Research
National Institutes of Health
Bethesda, MD 20892

RE: Request for Information (RFI) on Catalyzing the Development and Use of Novel Alternative Methods to Advance Biomedical Research

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Dear Working Group Members,

The Federation of American Societies for Experimental Biology (FASEB) appreciates the opportunity to provide comments on the Request for Information (RFI) (NOT-OD-23-140) regarding the development and use of Novel Alternative Methods (NAMs). As a coalition of 26 member societies across a broad range of scientific disciplines, we recognize the value of developing cutting-edge tools and resources to propel biomedical research forward, including both animal and non-animal models. Considering the rapid pace at which this field is advancing, FASEB appreciates the National Institutes of Health (NIH) Advisory Committee to the Director's (ACD) forward-thinking approach to investing and using NAMs in future biomedical research studies. However, given the many gaps and challenges associated with NAMs—further explained in our comments below—it is essential for the Working Group to emphasize in its final recommendations that animal models remain the premier method for numerous areas of research. Clarifying the research contexts in which NAMs may be appropriate and highlighting their role in *supplementing* work with animals is an important step in adjusting end-user and public expectations until validation strategies, metrics, and regulatory pathways become more defined.

FASEB has identified three central themes that can aid the Working Group and NIH in outlining future areas of investment:

- Establish uniform validation guidelines and consider parallel investments in validation studies when funding NAMs to ensure new technologies are well-characterized with clear endpoints and metrics.
- Develop and/or endorse NAM-specific reporting and data-sharing guidelines that acknowledge the rigor, reproducibility, and translatability challenges inherent in non-animal models.
- Strengthen partnerships and collaborations between federal agencies, industry, scientific societies, and animal researchers to exchange best practices, minimize regulatory burden, and ensure equitable and feasible implementation.

Please find FASEB's comments on each RFI topic and the above-mentioned themes below.

Topic 1: The use of novel alternative methods to study human biology, circuits, systems, and disease states.

a. **How NAMs are currently being developed and/or used successfully, including features that maximize scientific utility;**
b. **How NAMs are advancing progress into understanding specific biological processes or human states, including potential limitations to addressing human variability;**
c. **How NAMs could be truly revolutionary for understanding/treating human health, including currently underserved areas of biomedical research.**

FASEB Response:

1a. For NAMs to be effective, it is crucial to have ample evidence demonstrating their validity, replicability, and capacity to accurately reflect human biology and disease. While the field is in its infancy, NAMs have enabled fields such as toxicology to make remarkable advances. For example, the Environmental Protection Agency (EPA) is developing several in silico, in chemico, and in vitro approaches to evaluate skin sensitization, eye irritation, and inhalation risk assessments. Additionally, researchers at the Food and Drug Administration (FDA) recently developed a recirculating, in vitro flow loop system for thrombogenicity testing of medical devices (Sarode & Roy, 2019), an important step forward in mitigating blood clots in patients with blood-contacting medical devices. Common features that allowed these models to proceed through the development pipeline include sufficient data and testing, clear endpoints, rigorous benchmarking studies, and evaluation metrics.

To maximize scientific utility and achieve regulatory acceptance, continuous collection and evaluation of NAMs data through pilot programs and comparative assessments are essential. Ideally, FASEB recommends this process coincide with regular stakeholder meetings and public comment opportunities to exchange information and assess potential regulatory implications for end-users. Despite the tremendous promise of NAMs, federal agencies recognize that current non-animal systems cannot yet replace all animal studies. As a result, federal agencies like the EPA and FDA frequently launch pilot programs and/or case studies to study the predictivity of certain models before publishing draft policies and risk assessments. Because NAMs are largely in the development phase, this type of flexible and iterative approach is necessary to ensure the best available data informs agency decision-making. Therefore, in formulating next steps for NAMs research, FASEB urges NIH to leverage data collection opportunities (pilot programs, case studies, working groups, etc.) and public comment periods. This level of engagement could facilitate the agency's ability to redirect resources according to the latest science while ensuring that subsequent policy implementation reflects multiple stakeholder perspectives.

Topic 2: Approaches for catalyzing the development and validation of novel alternative method technologies.

a. **Challenges for building robustness, replicability, reproducibility, and reliability of technologies and the ensuing datasets;**
b. **Strategies for bolstering technology readiness and reliability of these technologies;**

c. Factors potentially limiting the successful integration of these technologies across research approaches and potential solutions.

FASEB Response:

2a-b. One of the primary challenges in building robust, reproducible, and reliable NAMs is the lack of validation data. This problem largely stems from the fact that there is no clear consensus on effective strategies for evaluating NAMs, resulting in the overall absence of uniform guidelines or criteria to conduct validation studies. As NIH outlines future areas of investment, FASEB strongly advises prioritizing the development of validation guidelines before allocating funding toward new technology development. Furthermore, to ensure model development and validation are considered concurrently, we recommend providing equal and parallel funding for validation studies alongside future NAM grants, initiatives, or projects. One potential approach to achieve this goal and reduce experimental bias is collaborating with external organizations to perform independent validation studies. FASEB recognizes that model validation—and scientific confidence more broadly—is a complex, time-consuming, and expensive process that requires standardized metrics, meaningful endpoints, benchmarking studies, as well as consultation with regulatory and public stakeholders. However, without consistent validation guidelines and confirmatory data from human and animal studies alike, the development of NAMs will continue to outpace scientific standards and applications, resulting in inefficient use of research time and federal dollars.

Additionally, data reporting requirements and transparency of results associated with NAMs research remain very limited, creating an additional challenge in establishing robust and reproducible alternatives. To develop safe and efficacious NAMs, the scientific community must have reliable, accessible information demonstrating that alternatives perform as well as or better than traditional animal studies. FASEB supports the recent recommendations from the previous ACD Working Group regarding ways to improve animal research rigor and reproducibility and applauds NIH's recent Guide notice (NOT-OD-23-057) encouraging the use of the ARRIVE Essential 10 in all publications resulting from vertebrate animal and cephalopod research. However, standardized reporting requirements for NAMs have not received equal attention or uptake. General frameworks and databases such as the Materials Design Analysis Reporting (MDAR) and the European Commission's Tracking System for alternative methods towards Regulatory acceptance (TSAR) represent useful steps forward, but are not broadly used and do not resolve the rigor and reproducibility shortcomings of NAMs.

Therefore, to ensure NAMs are evaluated with the same level of rigor and reproducibility as animal studies, FASEB recommends that NIH partner with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) "Validation Workgroup" to develop validation and reporting strategies for NAMs. The workgroup's charge could include conducting comparative studies with human and animal data (e.g., closest clinical data available) and establishing a set of minimum reporting requirements for publications. Because the current workgroup's scope is limited to toxicology, we recommend working with ICCVAM to expand this effort or create parallel groups focused on NAMs validation and reporting in biomedical research more broadly. Considering NIH's current participation in ICCVAM, FASEB considers this to be a suitable and streamlined approach to push the field forward while acknowledging the current regulatory, validation, and reporting constraints. Recognizing that the current ACD Working Group is developing a landscape analysis of the advantages and disadvantages of various NAMs, we suggest providing this information to the potential new group to inform next steps and ensure

harmonization across NAMs-related entities. Finally, this new workgroup may benefit from meeting regularly with industry groups, scientific societies, and other stakeholders to share data, best practices, and conduct independent validation studies.

2c. In addition to the absence of reporting requirements, a major challenge in successfully integrating novel technologies across research approaches is the lack of funding mechanisms available to study model characterization, particularly for novel technologies. To effectively validate NAMs, a thorough understanding of how a model functions is essential. This includes identifying mechanisms of action, scientific context of use, and risk of bias. However, characterization studies are often not considered "fundable" activities, resulting in delays in their widespread use and relevance. As the Working Group articulates high-priority areas for NIH investment, FASEB advises exploring ways to modify current funding opportunities to accommodate this gap in the field or create new funding mechanisms specifically dedicated to NAM characterization.

A second challenge is the considerable time and costs to conduct nonanimal studies. This often varies in different sectors depending on discipline-specific needs and the complexity of the research question. To inform NIH's future investment strategy in NAMs, FASEB recommends conducting cost-effective analyses of proposed technologies with existing methods, including animal studies. Specific aspects to consider through these analyses include time, scalability, and resource efficiency. Not only will the costs associated with scaling NAMs for broad deployment be significant, but in many cases, combinations of multiple NAMs may not necessarily outperform single tests involving animals, further increasing costs. Although such analyses will require substantial time and effort to complete, this information ensures proper stewardship of future federal investments and can facilitate the public's understanding of the current NAMs landscape.

Another factor restricting the integration of NAMs across the biomedical research enterprise is insufficient engagement between regulators, NAM developers, and end-users. While current federal agency efforts are laudable—including the EPA NAMs Work Plan, the FDA Alternative Methods Working Group, ICCVAM, and the National Center for Advancing Translational Sciences (NCATS)—this piecemeal approach prohibits the formation of a cohesive and shared knowledge base. Therefore, FASEB strongly recommends strengthening interagency partnerships to develop a coordinated NAM approach that enables science to advance efficiently while minimizing administrative and regulatory burden. One early goal to work towards through these partnerships is developing a strategic plan with milestones to align NAM research priorities across the various federal entities. Additionally, we encourage interagency collaborations to leverage the expertise of end-users and professional societies through workshops and comment periods. This is an essential step towards advancing the scientific community's commitment to the 3Rs and promoting an open dialogue about complex research topics.

<u>Topic 3:</u> Strategies for maximizing the research value of novel alternative method technologies.

- **a. Areas in which coordinated approaches across research disciplines or research sectors would dramatically advance the development and/or use of these technologies;**
- **b. Approaches for sharing technology deployment equitability across labs, including incentives for reliable and reproducible methods integration;**
- **c. Factors for consideration when maximizing translatability and minimizing bias regarding human variability.**

FASEB Response:

3b. To ensure equitable distribution of resources across labs, it is essential to have access to scientific information and adequate support for research staff and infrastructure. As noted earlier, developing minimum reporting standards for NAMs represents a crucial step in improving rigor, reproducibility, and transparency in this field. However, another benefit of an accepted set of reporting standards is improved access and sharing of cross-disciplinary knowledge and expertise. This will enable research labs of all sizes and capacities to prioritize future research topics, acquire appropriate resources, and identify potential collaborators.

Secondly, FASEB recommends NIH provide additional support for research infrastructure, shared resources, and technical staff to promote fair allocation and access to animal and non-animal methodologies. In many cases, particularly for resource-limited institutions, researchers lack the necessary tools and expertise to utilize novel technologies essential to their field and career development. Suggested strategies for addressing this gap include increasing infrastructure grants (G20, C06) to enable institutions to build state-of-the-art facilities and expanding the number of shared technology hubs—such as those funded through the National Institute of General Medical Sciences (NIGMS) National and Regional Resources R24 program—to areas with historically less NIH funding. Specific funding and career development opportunities are needed for core facility and technical staff to ensure scientific expertise keeps pace with rapid technology development, including NAMs. One way to achieve this is expanding opportunities for trainees on F-, K-, and T- grants to facilitate their exposure and training with novel methods. To achieve efficient and equitable technology sharing, FASEB urges NIH to harness the full potential of core facilities, shared resources, and staff scientists. Because non-animal model development and validation are critically dependent on animal studies for the foreseeable future, FASEB considers these recommendations as opportunities to advance animal and non-animal research simultaneously.

3c. Maximizing the translatability of NAMs and reducing inherent biases requires implementing standards for rigor and reproducibility, as well as fostering collaboration across different disciplines. As noted in question 2a-b, FASEB recommends prioritizing the development of uniform guidelines that NAM developers and users can use to support validation studies and evaluate scientific confidence of these models. This effort serves as an opportunity to strengthen collaborations with other federal agencies and appropriately complements our previous recommendations to fund parallel validation studies and create minimum reporting standards. If possible, guidelines should be consistent across federal agencies to streamline NAM development and validation while minimizing end-user administrative burden.

Recent work from ICCVAM and the National Academies of Sciences, Engineering, and Medicine (NASEM) can provide valuable insights to achieve this goal. For example, ICCVAM published a recent framework (van der Zalm, 2022) for establishing scientific confidence in NAMs that outlines five essential elements for determining their adequacy: fitness for purpose, human biological relevance, technical characterization, data integrity and transparency, and independent review. While the authors note that the focus is primarily on pesticides and industrial chemicals, the framework is intended to be adaptable to other fields. As another example, NASEM recently published a report, *Building Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests,* that outlines the various barriers to broad deployment of NAMs in EPA-related decision-making. Similar to the ICCVAM framework, the report highlights five components for building

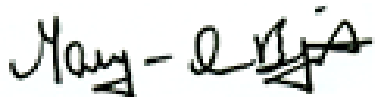
scientific confidence in NAMs: intended purpose and context of use, internal validity, external validity, biological and experimental variability, and transparency. The discrepancies between the two documents—as well as other resources— demonstrate the need for interagency partnerships to build unified guidelines with a shared vocabulary, definitions, and objectives that can propel innovation forward.

Finally, to optimize translatability in an evidence-based manner, FASEB recommends NIH develop new mechanisms to foster collaboration between animal researchers and NAM developers. Another recent NASEM report, *Nonhuman Primate Models in Biomedical Research*, underscores how nonhuman primates (NHPs) remain essential for NIH-supported biomedical research given the lack of qualified and validated NAMs to answer complex research questions. To address this, the report emphasizes the importance of enhanced collaboration between NHP researchers and NAMs developers to expand the applicability of non-animal systems. FASEB concurs with the report's suggested strategies for accomplishing this and encourages NIH to establish multi-laboratory funding opportunities, cross-disciplinary challenge programs, and annual conferences or symposia that mobilizes varying perspectives and expertise. For the latter, we strongly advise partnering with scientific societies to leverage their knowledge and networking capabilities for maximal impact and effective policy implementation.

Conclusion

FASEB appreciates the opportunity to offer comments on strategies for maximizing the development and use of NAMs. Stakeholder feedback is central to sound policymaking. As scientists that strongly support the use of various resources to advance biomedical research, including humane animal studies and non-animal models, we look forward to future engagement opportunities on this topic and the Working Group's final recommendations.

Sincerely,



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