ASPET
Transforming Discoveries into Therapies

August 16, 2023

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

Submitted online via RFI website on August 16, 2023.

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

Dear Working Group Members,

On behalf of the members of the American Society for Pharmacology and Experimental Therapeutics (ASPET), we appreciate the opportunity to provide comments on the Request for Information (NOT-OD-23-140) seeking input on challenges and opportunities for the further development and use of novel alternative methods (NAMs) in biomedical research.

ASPET is a 4,000-member scientific society whose members conduct basic and clinical pharmacological research and work in academia, government, industry, and non-profit organizations. ASPET members conduct research leading to the development of new medicines and therapeutic agents to fight existing and emerging diseases. ASPET is a global pharmacology community that advances the science of drugs and therapeutics to accelerate the discovery of cures for disease. We are in constant pursuit of our Mission through research, education, innovation, and advocacy.

Over the last few decades, the development of cutting-edge tools that use non-animal based approaches for pharmacological advances has been rapid. Between 2016 and 2021, the FDA has seen a large increase in the number of submissions that included *in silico* tools, specifically artificial intelligence (AI) and machine learning, in research informing drug discovery and repurposing, as well as enhancing clinical trials among others. Therefore, ASPET 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.

Despite ASPET's enthusiasm about the potential NAMs have in advancing pharmacology, toxicology, and future therapeutics, we are very privy to the limitations of NAMs. The Working Group, therefore, should highlight in its final recommendations that animal models remain the premier method for many areas of research, clarifying where the use of NAMs is appropriate or necessary to supplement the use of animal models as the field continues to identify and overcome the current challenges it has to provide adequate data.

Below you can find ASPET's comments on each RFI topic:

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

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

Many studies in pharmacology and toxicology have been utilizing NAMs to advance our understanding of toxic substances, risk assessments, and drug development, especially with the most recent rapid developments in machine learning and AI technologies. Many groups are adopting the reduce, refine and replace animal use in research studies. Using NAMs with sufficient data, testing, and evaluation metrics are the hallmarks of what allowed these models to proceed through the development pipeline.

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

- **Challenges for building in robustness, replicability, reproducibility and reliability of the technologies and the ensuing datasets;**
- **Strategies for bolstering technology readiness and reliability these technologies; and**
- **Factors potentially limiting the successful integration of these technologies across research approaches and potential solutions.**

ASPET believes that in order to build more confidence in the performance, replicability and reproducibility of NAMs in order to reliably use them, there needs to be clear consensus on effective strategies for evaluating and standardizing them and their use. A current challenge is the absence of guidelines or criteria to conduct validation studies on different types of NAMs. NIH should prioritize the development of validation and standardization guidelines before allocating funding toward new technology development. This should include emphasis on NAMs data confirmatory with human and animal studies and developing new mechanisms to foster collaboration between animal researchers and NAMs developers to perform validation studies. Moreover, strengthening interagency partnerships to develop a coordinated NAMs approach that enables science to advance efficiently while minimizing administrative and regulatory burden.

Other challenges to building in robustness, replicability, reproducibility and reliability of NAM include data reporting requirements for NAM studies, as well as the time and costs to conduct non-animal studies, although the latter can vary by discipline and sector. ASPET recommends conducting cost-effective analyses of proposed NAMs with existing methods like 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 where animals are used.

Topic 3: Strategies for maximizing the research value of novel alternative method technologies.

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

As mentioned before, to qualify NAMs for regulatory use, more robust data collection, evaluation, and standardization of NAMs is needed. One way to achieve that is through pilot programs and comparative assessments across disciplines and sectors. Most of the current non-animal models are still in the development stage and cannot yet replace all established animal models. Launching pilot and/or case studies to study the predictivity of certain models before publishing draft policies and risk assessments, as currently done by some agencies like FDA and EPA, is a great flexible approach that can help ensure that the best available data informs agency decision-making. Therefore, as NIH formulates the next steps for NAMs research, ASPET recommends employing data collection opportunities like the mentioned pilot and case studies to help redirect resources according to the latest science while ensuring that subsequent policy implementation reflects multiple stakeholder perspectives.

ASPET also recommends that NIH provides support for research infrastructure, shared resources, and technical staff to promote fair allocation and access to animal and non-animal methods for conducting research. This is because using novel technologies requires resources and training use such methods that resource-limited institutions may not have. To address this, NIH may consider increasing infrastructure grants (G20, C06) to enable institutions to build facilities to keep up the emerging technologies. Moreover, providing targeted funding and career development staff scientists 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.

In conclusion, we thank the NIH for their continued efforts to identify areas in which the development and use of NAMs provide the most value to biomedical research and we look forward to future updates and engagement opportunities on this topic and the Working Group's final recommendations.