Background and Glossary

Background

While animal studies remain foundational for advancing scientific knowledge and developing therapeutics, there is increasing recognition that animal models are often suboptimal at predicting human physiological and pharmacological responses due to species-specific differences. At the same time, there have been critical advances in human-based NAMs that have the potential to transform our understanding of human health and disease pathways. While many NAMs are still in early stages of development, they have potential to promote translation of basic research to clinical application across various populations with differing susceptibilities (e.g., genetic, epigenetic, environmental exposure). The past decade has seen dramatic advances in areas such as complex in vitro systems (Microphysiological systems (MPS)/tissue-chips, organoids, induced pluripotent stem cells (iPSCs)), bioengineering technologies (e.g., CRISPR/Cas-9, single-cell sequencing, spatial "omics", phenotypic profiling, cyborg tissues), human data (e.g., electronic health records (EHR), digital twins, sensors, geospatial mapping), and computational methods (e.g., multi-scale modeling, cognitive algorithms, artificial intelligence/machine learning (AI/ML)). Existing programs in the Common Fund Data Ecosystem and others (e.g., MPS-Database, Bridge2AI, All of Us) represent a wealth of data to support and enable human-based NAM approaches that can complement animal models. These emerging tools, technologies, and data sources could be leveraged and integrated to identify solutions that can considerably advance NAMs and their widespread adoption.

In response to the rapid growth of NAMs technologies, the NIH conducted strategic planning activities to inform the Complement-ARIE program, which aims to speed the development, standardization, validation, and use of human-based NAMs. These included three public listening sessions that brought together key representatives from multiple sectors, an interagency retreat with federal partners to discuss high-priority areas, and a landscape analysis to ensure Complement-ARIE is focused on areas of greatest scientific need and human-based model development.

From these strategic planning efforts, the Complement-ARIE program developed three pillars:

1. **Technology Development Centers**

Technology Development Centers (TDCs) will be NAMs development centers focused on high priority areas of greatest need, with emphasis on biological complexity, throughput, innovative combinatorial approaches, capture of population variability and susceptibility, and resource and data sharing according to FAIR (findable, accessible, interoperable, and reusable) principles. Ideally, TDCs will generate mature combinatorial NAMs with clinical utility for defined use cases that will progress to validation and qualification in partnership with regulatory authorities and industry.

2. **NAMs Data Hub and Coordinating Center**

The NDHCC will integrate data structures via a central data hub. This will help to develop and apply standards for data reporting and model credibility and improve FAIR adherence by NAM-relevant data, including data interoperability and data-reuse strategies. The NDHCC will create a searchable NAMs repository, develop tools for data analytics, and lower barriers for sharing NAMs-related data with researchers and the wider community.

3. **Validation and Qualification Network**

Successful adoption of NAMs for biomedical, preclinical, and regulatory use requires that all sectors with appropriate skills and resources work together in innovative and collaborative ways to accelerate NAMs validation. Accordingly, the NIH, in collaboration with the Foundation for the NIH (FNIH) is in the process of establishing the VQN through a Public-Private Partnership (PPP) involving scientists at multiple levels of government (including funding agencies and regulators), industry, nongovernmental organizations, and academic institutions. By their shared expertise, the VQN will be designed to uniquely catalyze the development, standardization, and validation of human-based NAMs.

The VQN will establish a process for evaluating NAMs and channeling use cases through its framework in a pre-competitive environment, paving the way for broader adoption and application by industry and biomedical researchers globally.

For clarity, the VQN does not have any legal or regulatory authority and, therefore, cannot validate and/or qualify any specific NAMs with **regulatory** context(s) of use. It should be noted that "validation" has a specific meaning associated with FDA's medical product regulation, beyond the term's common use related to "scientific validation."

Complement-ARIE also launched an Ideation Challenge, which spurred submissions of innovative ideas to help define what types of NAMs could benefit from further investment. The Ideation Challenge drew a range of submissions from industry groups and academia, often combining researchers from different fields such as bioengineering, chemistry, data science, and clinical medicine. These groups represented non-traditional NIH applicants and indicated the broader outreach that a prize competition could achieve.

As a subsequent Challenge to the Ideation Challenge, the **Reduction-to-Practice Challenge** seeks integrated solutions that are fully implementable through a phased approach. This Challenge emphasizes the combination and integration of multiple (more than one) NAMs methods (combinatorial NAMs) to create cohesive solutions for comprehensive insight into human biology and is focused on addressing areas of greatest scientific and regulatory need. This Challenge follows the recent NIH announcement to prioritize human-based research technologies and reduce reliance on animal models. The FDA released a similar announcement describing its initiative to reduce animal models in testing alongside a strategic roadmap to implement the use of NAMs in preclinical safety studies. In alignment, the EPA has an existing strategic plan promoting alternative test methods to reduce the use of vertebrate animal testing. As such, this RTP Challenge presents a timely opportunity to spur collaboration within the scientific and industrial community to develop transformative human-based approaches. NIH hopes this Challenge will demonstrate new ways of predicting human responses to disease and/or environmental exposures (i.e. drugs or chemicals), improving healthcare outcomes, and delivering product safety.

Innovators are tasked in this open competition to accelerate technological development of a combinatorial NAMs platform and translate their products into practice. Successful teams for this Challenge will likely consist of large, multi-disciplinary groups with expertise in all Phases as described by the Challenge.

Glossary

- *In vitro* models: three-dimensional (3D) human-derived tissue or cell culture technologies that more closely resemble *in vivo* cell environments that may include use of spheroids, organoids, bioprinted constructs, tissues/organs-on-chips or microphysiological systems.

- *In silico*: computational models that incorporate biological data with mathematical and computer-based representations to construct models of human biology using methods such as data analyses, data mining, homology models, machine learning, pharmacophores, quantitative structure-activity relationships, and network analysis tools.

- *In chemico*: cell-free systems that can recapitulate, probe, or augment normal cellular, tissue, or organismal processes, for example, reactive abiotic chemical methods that test the properties of substances, recombinant artificial membranes to model metabolite or drug transport, or synthetic biology approaches to produce macromolecules with human-like post-translational modifications.

- *Combinatorial NAMs*: The combination and integration of multiple (two or more) NAMs elements into a synergistic approach that augments gaps and/or deficiencies in individual NAMs approaches, ultimately allowing for improved predictions of human clinical response.

- *Reduction to Practice*: Successfully demonstrating that an invention or concept can be implemented in a practical and usable form.

- *Validation* – Validation is a process of establishing documentary evidence demonstrating that a procedure, process, or activity carried out in production or testing maintains the desired level of compliance at all stages and will consistently produce the expected results

- *Context of use (CoU)* - Clearly articulated description delineating the manner and purpose of use for a particular method or approach. Having a more specific CoU greatly aids the validation and/or qualification process

- *Fit-for-purpose* - “Suitable and appropriate for a technology’s intended use”

- *Qualification* - Within a stated CoU, qualification is a conclusion that the results of an assessment using a model or assay can be relied upon to have a specific interpretation and application. Qualification must identify the boundaries of the available data that adequately justify the use of the tool. The qualification process evaluates the fitness of the model for a

specific CoU, with characterization of the challenge agent(s) and exposure, primary and secondary endpoints, triggers for intervention, and key disease values to be replicated for quality assurance and control.

- **FAIR**: findable, accessible, interoperable, reusable data.
  - Findable: For data to be findable there must be sufficient metadata; there must be a unique and persistent identifier; and the data must be registered or indexed in a searchable resource.
  - Accessible: To be accessible, metadata and data should be readable by humans and by machines, and it must reside in a trusted repository.
  - Interoperable: Data must share a common structure, and metadata must use recognized, formal terminologies for description.
  - Reusable: Data and collections must have clear usage licenses and clear provenance and meet relevant community standards for the domain.
- **Personalized medicine**: also known as "precision medicine" is an innovative approach to tailoring risk assessment, diagnosis, and disease prevention and treatment based on an individual's genetics, environment, lifestyle, age, and diet/nutrition. It aims to provide the right treatment for the right patient at the right time, considering these factors.
- **Technical Readiness** – Readiness demonstrated by a new or novel technology. For example, biomedical products technical readiness levels (TRLs) are categorized as follows:

TRL 1 (Basic Principles Observed): Scientific knowledge is generated and assessed as a foundation for new technologies.

TRL 2 (Technology Concept or Application Formulated): Practical applications are identified, and research plans are developed.

TRL 3 (Analytical and Experimental Proof of Concept): Laboratory studies and simulations validate the technology's feasibility.

TRL 4 (Lab Demonstration): Components and systems are tested in a laboratory setting.

TRL 5 (Lab Scale Validation): Prototypes are validated in a relevant environment.

TRL 6 (Prototype Demonstration): A fully functional prototype is tested in a realistic environment.

TRL 7 (Pilot System Demonstrated): The technology is tested in an operational environment.

TRL 8 (System Incorporated in Commercial Design): The technology is fully developed and tested.

TRL 9 (Proven System Ready for Deployment): The technology is ready for commercialization and use in real-world settings.

- See provided links for examples: [Link 1] [Link 2]