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FDA's Continued Approach to Implementing NAMs: What Sponsors Need to Know

The regulatory conversation around New Approach Methodologies (NAMs) is changing. In April 2025, the Food and Drug Administration (FDA) outlined a stepwise roadmap to reduce the reliance on animal testing and expand NAMs in drug development (1). Since then, the FDA has begun turning that vision into practice by identifying where traditional studies may be streamlined, reduced, or replaced, clarifying how NAMs and models should be evaluated, and creating opportunities for sponsors to seek feedback before using them in major development decisions (2–6).

A NAM needs to address a defined scientific or development question, reflect relevant human biology, produce sufficiently reliable evidence, and be appropriate for the decision it is intended to support (3). For sponsors, this creates opportunities to streamline traditional testing strategies. It also places greater emphasis on scientific justification, context of use, documentation, uncertainty, and early regulatory engagement.

In this article, we explore how the FDA's approach to NAM implementation is evolving, what that means for organizations considering computational models, PBPK, in vitro methods, and other non-animal approaches, and how ScitoVation can help.

Key Developments in FDA's Approach to NAM Implementation

1. Moving from support for NAMs to practical implementation

The FDA's Center for Drug Evaluation and Research (CDER) has moved from broad support for NAMs toward clearer guidance on their practical use. CDER has identified situations where sponsors may be able to reduce the number of animals, species, or separate studies used in development, combine safety endpoints, or use weight-of-evidence approaches in place of some traditional testing (2).

Those assessments may integrate information from pharmacology, prior knowledge, clinical and nonclinical evidence, modeling, and non-animal methods. The FDA's March 2026 draft guidance adds an important principle that a NAM should be evaluated in relation to the question and context in which it will be used (3). That means asking:

- Does the method reflect the biology relevant to the development question?
- Does it produce sufficiently reliable results?
- Is it appropriate for the proposed context of use?

A NAM does not necessarily need to be formally validated before it can be considered for review in drug development. A fit-for-purpose NAM may still contribute meaningful evidence within a weight-of-evidence assessment. However, the FDA also emphasizes that validation

considerations remain important for establishing reliability, relevance, and appropriate interpretation in the intended context of use (3).

These developments also support the 3Rs: replacement, reduction, and refinement. FDA's 2025 roadmap set out a strategy to reduce animal testing through human-relevant alternatives, while subsequent implementation activities have identified situations where studies may be replaced, animal use reduced, or existing approaches refined (1,2). Importantly, NAMs do not need to replace traditional studies one-for-one; they may also contribute as part of an integrated weight-of-evidence strategy.

2. Start with the decision

The same principle appears in the regulatory framework for model-informed drug development. The final ICH M15 guideline provides a harmonized framework for planning, evaluating, and documenting model-informed drug development approaches, including PBPK, exposure-response analysis, quantitative systems pharmacology and toxicology, and other modeling approaches (6).

Rather than outlining one way to build or evaluate a model, ICH M15 asks sponsors to define how the model will be used. Its intended use, influence on the decision, and the consequences of an incorrect result help determine the level of evaluation, documentation, and uncertainty assessment required (6). In practical terms: What decision are we trying to make, how much weight will the model carry, and what happens if it is wrong?

FDA's Model-Informed Drug Development Paired Meeting Program also provides selected sponsors with an opportunity to discuss modeling strategies with the CDER or CBER in the context of specific drug-development questions (4). Early dialogue can be particularly valuable when a novel or nontraditional approach is expected to have a meaningful influence on a development decision.

3. Weight-of-evidence approaches are becoming more tangible

FDA's May 2026 draft guidance for certain oncology biologics and conjugated products provides a practical example of how these principles could change development programs. The guidance focuses on opportunities to streamline nonclinical toxicology programs. Depending on the circumstances, sponsors may be able to eliminate an unnecessary animal study, use a single relevant species rather than two, or use a weight-of-evidence assessment in place of a traditional three-month study (5).

That assessment may bring together pharmacology, clinical and nonclinical data, prior knowledge, and fit-for-purpose NAMs (5). Rather than serving as isolated replacements for individual tests, NAMs may contribute as part of an integrated evidence package. This allows sponsors to consider what evidence already exists, what uncertainty remains, and whether modeling or non-animal methods could address that uncertainty before another conventional study is commissioned.

4. NAMs are already appearing in regulatory submissions, but weaknesses remain

Recent FDA-authored publications indicate that NAMs are already being used in drug-development programs and regulatory submissions. FDA reviewers have documented examples where NAMs have replaced animal tests, contributed to individual regulatory decisions, or provided supporting evidence within development programs (7). A separate CDER analysis found that 93% of the identified NAM submissions were in silico or in vitro, while organ-on-chip and microphysiological-system approaches remained comparatively uncommon (8).

Regulatory experience also highlights recurring weaknesses, including unclear context of use, limited biological relevance, insufficient technical characterization, and incomplete reporting (7). A sophisticated method may still provide weak support if its intended use is unclear or reviewers cannot understand how the result was generated and interpreted. On the other hand, a fit-for-purpose method with transparent documentation and clearly described limitations may contribute meaningfully to a broader weight-of-evidence assessment.

The July 28 FDA, Health and Environmental Sciences Institute (HESI), and Safety Pharmacology Society (SPS) workshop further highlights how quickly the field is evolving. The meeting explored the scientific rationale for a possible revision of ICH S7A, including opportunities, constraints, and potential roles for NAMs in safety pharmacology (9). Overall adoption is advancing, but the scientific and regulatory frameworks surrounding broader implementation are still developing.

What does this mean for organizations adopting NAMs?

The emerging regulatory direction points to several practical priorities:

1. **Start with the decision:** Define the development or safety question before selecting the method. Use a NAM, PBPK model, or other computational approach because it provides relevant evidence, not just because the technology is available.
2. **Establish human relevance:** Show how the method connects to the biology, dose, or exposure conditions that matter for humans. This may require integrating multiple evidence streams.
3. **Make uncertainty and assumptions visible:** Models and NAMs do not need to eliminate uncertainty to be useful, but assumptions, applicability limits, technical performance, and potential consequences of error should be clearly documented and communicated.
4. **Prioritize reproducibility and data integrity:** Underlying data, analytical procedures, and outputs should be sufficiently controlled and documented so results can be reproduced, reviewed, and trusted.

5. **Engage regulators early where the stakes are high:** Early engagement can help clarify expectations when a novel method is expected to influence an important development decision.
6. **Look for opportunities across all three Rs:** Consider where NAMs can replace a study, reduce animal use, or refine an existing strategy by providing more targeted, human-relevant evidence.

How ScitoVation can support this transition

The increasing use of NAMs does not eliminate the need for scientific judgment. In many cases, it increases the importance of selecting the right method, integrating different forms of evidence, and explaining how each piece contributes to the decision.

ScitoVation helps organizations connect computational and non-animal approaches to the specific safety or development question they need to answer. This can include bringing together existing scientific evidence, identifying decision-critical data gaps, evaluating human relevance, applying PBPK and qIVIVE approaches, interpreting transcriptomic evidence, and structuring the resulting information into a clear scientific or regulatory narrative.

The aim is not to use a NAM simply because it is newer or faster. It is to determine whether the method provides credible evidence for the question at hand, understand its assumptions and limitations, and show how it contributes to the overall weight of evidence. As FDA's approach continues to evolve, the connection between method, context of use, human relevance, uncertainty, and decision is likely to become increasingly important.

Conclusion

Animal studies will not disappear immediately, and regulatory acceptance of NAMs will remain dependent on the method, supporting evidence, and context in which it is being used. What is changing is the pathway to implementation. The FDA is providing clearer guidance on fit-for-purpose use, creating opportunities for earlier discussion of novel approaches, publishing examples of NAM use in regulatory submissions, and identifying circumstances where integrated evidence may reduce, refine, or replace traditional animal studies.

For sponsors, the opportunity goes beyond replacing one test with another. It is to build more efficient evidence strategies in which NAMs, modeling, PBPK, existing knowledge, and other data sources are selected and integrated according to the decision they need to support.

ScitoVation can help organizations navigate that process by connecting emerging methods to human relevance and building transparent, scientifically defensible evidence packages.

If you are considering where NAMs, PBPK, or computational approaches could fit within your safety or development strategy, [talk to a scientist](#). We can help identify where these methods can add meaningful evidence, where limitations need to be addressed, and how to integrate them into scientifically rigorous, transparent, regulator-ready strategies.

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