Why Did FDA Accept One NAM or AI-Based Approach but Reject Another?

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The SAPA-DC 2026 Scientific Symposium was held on June 13, 2026, in North Bethesda, Maryland. The event featured 15 speakers and brought together approximately 100 participants from FDA, NIH, academia, and industry to discuss advances in New Approach Methodologies (NAMs), organoid technologies, artificial intelligence (AI), and regulatory science. Remote access was also provided for attendees unable to participate in person.

A common theme emerged across the presentations: the key regulatory question is no longer whether a technology is animal-based or non-animal-based, nor whether AI can generate predictions. Instead, the critical question is whether the evidence generated is reproducible, validated, and fit for its intended context of use (COU). Several presentations approached this challenge from complementary perspectives: FDA regulatory decision-making, NIH-led validation frameworks, and advanced human tissue model development.

1. Why Did FDA Accept One NAM or AI but Reject Another?

Drug development is governed by legislation, regulations, and guidance. While FDA and other regulators are increasingly encouraging NAMs, regulatory acceptance remains context dependent. My presentation reviewed the 2024 Vanda v. FDA lawsuit, in which the court upheld FDA's authority to require long term animal safety data. This case demonstrated that NAMs do not automatically replace animal studies; their acceptance depends on whether they adequately answer the regulatory question.

This principle was further illustrated by FDA case studies comparing a rejected human airway model with the successful use of NAM data for Kimmtrak. The airway model was not accepted because of limited biological complexity and insufficient validation, whereas Kimmtrak successfully relied on human-relevant assays when no pharmacologically relevant animal model existed. Additional evidence came from a 2026 FDA analysis of 23 IND submissions showing that hiPSC-derived cardiomyocyte assays demonstrated strong predictive performance for QT prolongation, supporting the use of NAMs in appropriately defined contexts.

The presentation also reviewed the FDA 2025 AI guidance, 'Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products.' The guidance outlines a seven-step credibility assessment framework emphasizing context of use, model risk, validation, and documentation. Successful examples included the FDA-authorized Paige Prostate digital pathology system. In contrast, an FDA warning letter demonstrated that AI-generated output remains subject to existing GMP requirements and human oversight. Collectively, these examples suggest that FDA is not rejecting NAMs or AI; FDA is rejecting evidence that lacks sufficient validation, reproducibility, or fitness for purpose.

2. NIH SOM: Solving the Validation Problem

The NIH Standardized Organoid Modeling (SOM) Initiative can be viewed as a direct response to the validation and reproducibility challenges highlighted in FDA NAM case studies. While organoids have tremendous potential as human-relevant models, inconsistent protocols and variable performance across laboratories have limited their broader adoption and regulatory utility.

SOM focuses on standardizing organoid systems for liver, heart, lung, intestine, and other tissues while developing fit-for-purpose validation frameworks. The initiative aims to define acceptable variability, performance benchmarks, reproducibility boundaries, and model limitations based on specific contexts of use. The program brings together academia, industry, and regulatory agencies, including FDA, to establish greater confidence in organoid-based NAMs.

AI and machine learning are integrated into iterative workflows to optimize culture conditions, analyze high-dimensional datasets, and improve model performance. Regulatory milestones highlighted in the presentation included the FDA Roadmap to Reducing Animal Testing in Preclinical Safety Studies and the FDA iSTAND Pilot Program. The central message was that the primary challenge is no longer generating organoids but

demonstrating that they can reliably produce evidence suitable for regulatory decision-making.

3. NCATS 3D Tissue Models: Building the Human-Relevant Platform

If FDA regulatory science defines the acceptance criteria and SOM develops validation frameworks, the NIH NCATS 3D Tissue Bioprinting Program represents the technology platform that generates the models themselves. Marc Ferrer presented a portfolio of advanced human 3D tissue systems including spheroids, organoids, engineered scaffolds, tissue chips, and multi-organ chips designed to better represent human biology than traditional experimental models.

NCATS has developed models representing retina, skin, lung, placental/fetal barrier, cardiac tissue, brain, neurovascular unit, liver, and neuromuscular junction. Applications include disease modeling, efficacy evaluation, safety assessment, and regulatory science. Examples included neural spheroids for Parkinson's disease, Alzheimer's disease, addiction, and viral infection, as well as bioprinted hydrogel-based tissues designed to improve reproducibility and experimental control.

The presentation highlighted FDA Modernization Act 2.0 and emerging FDA NAM guidance as indicators of growing regulatory interest in human-relevant technologies. Key regulatory concepts included Context of Use, Human Biological Relevance, Technical Characterization, and Fit-for-Purpose. These are the same principles that ultimately determine whether innovative models will be accepted for regulatory decision-making.

Take-Home Message

Together, the three presentations described different parts of the same ecosystem. NCATS is developing increasingly human-relevant models. NIH SOM is building validation frameworks to ensure these models are reproducible and reliable. FDA is establishing the regulatory standards that determine whether the resulting evidence can support decision-making. The future challenge is no longer whether NAMs and AI can generate data, but whether they can generate evidence that is reproducible, validated, and fit for regulatory decision-making.

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