From Policy to Practice:

How Regulatory Momentum for New Approach Methodologies Is Accelerating the Adoption of Organ-on-a-Chip Technology

A Turning Point for Drug Development Models

The biopharmaceutical industry is at an inflexion point. For decades, animal models have served as the backbone of preclinical research, supporting target validation, efficacy assessment and safety evaluation. While these models have enabled countless therapeutic advances, their limitations in predicting human outcomes are increasingly well documented. Persistent late-stage attrition, unexpected toxicities and species-specific differences continue to highlight the translational gap between preclinical promise and clinical reality.

At the same time, a diverse set of human-relevant scientific tools has matured rapidly. Collectively referred to as New Approach Methodologies (NAMs), these approaches are reshaping how researchers think about safety and efficacy assessment. The term "New Approach Methodologies" was formally introduced in 2016 to describe a broad range of techniques, technologies and strategies designed to inform regulatory decision-making without relying on animal testing. While the acronym "NAMs" is sometimes informally used to mean "non-animal methods" or "new alternative methods," its regulatory meaning is more specific. NAMs are fit-for-purpose approaches that generate data relevant to hazard identification, risk assessment or safety evaluation in a manner that can support regulatory review.

Importantly, NAMs are not a single test or platform. Rather, they encompass a wide scientific ecosystem, including:

- *In vitro* systems, such as human cell–based assays, 3D organoids and microphysiological systems, including Organ-on-a-Chip technologies
- *In silico* models, including quantitative structure – activity relationship (QSAR) models, physiologically based pharmacokinetic (PBPK) simulations and artificial intelligence or machine learning approaches
- Omics technologies, such as transcriptomics, proteomics and metabolomics, which provide mechanistic insight into biological responses
- In chemico assays, which assess chemical reactivity directly
- Integrated frameworks, such as Integrated Approaches to Testing and Assessment (IATA), that combine multiple data streams into weight-of-evidence evaluations

What unites these diverse approaches is not simply the absence of animal use, but a shared emphasis on human-relevant biology, mechanistic understanding and data integration.

Within this broader NAM landscape, Organ-on-a-Chip technology has emerged as a particularly compelling solution. By combining human cells with microengineering, controlled fluid flow and physiologically relevant mechanical cues (Figure 1), these platforms seek to replicate key aspects of organ-level function *in vitro*. They represent a bridge between traditional cell culture and whole-organism biology, offering dynamic, tissue–tissue interfaces and functional readouts that were previously difficult to capture outside of animal models.

The growing sophistication of NAMs such as Organ-Chips coincides with a shift in regulatory policy and scientific priorities. Agencies in the United States, the United Kingdom and other regions have signalled increasing openness to alternative approaches and have articulated structured plans to expand their use. This convergence of technological maturity and regulatory momentum marks a turning point. The key question facing the industry now is not whether NAMs will play a role in the future

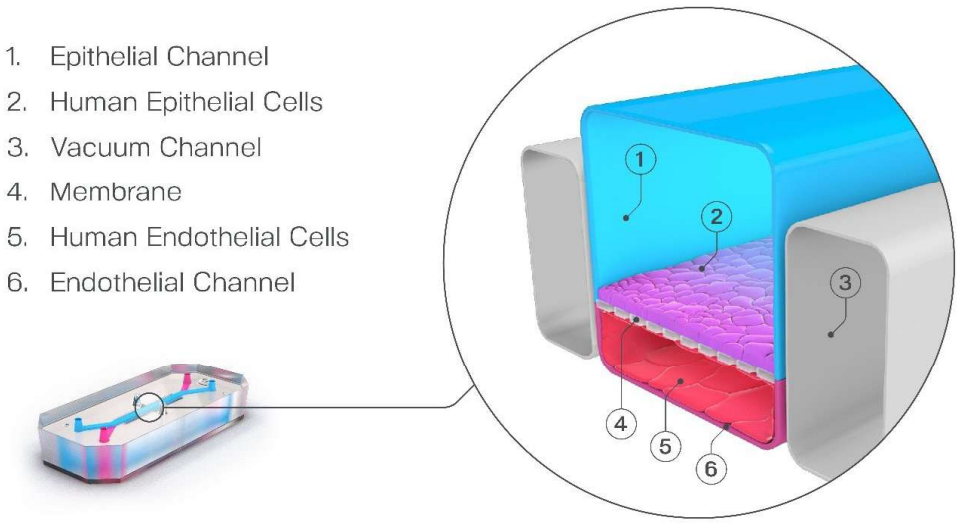


Figure 1: Diagram of an Organ-Chip. The original Organ-Chip design, Chip-S1 Stretchable Chip, consists of two parallel microfluidic channels (1, 6), with distinct channels for epithelial cells (2) and endothelial cells (5) and their respective cell culture media. A porous membrane (4) separates the two channels while enabling inter-channel communication and cell migration. Vacuum channels (3) alongside the microfluidic channels provide tunable mechanical stretch across the membrane. Image credit: Emulate, Inc.

of drug development, but how quickly and strategically they will be integrated and how the balance between traditional animal models and human-relevant systems will evolve in the years ahead.

Regulatory Signals:
From Encouragement to Structural Change

Regulatory agencies have long endorsed the principles of the 3Rs (replacement, reduction and refinement of animal use in research), but a pivotal change occurred in the United States with the passage of the FDA Modernization Act 2.0 in late 2022. It removed the explicit mandate that required the use of animal models in preclinical studies, instead allowing sponsors to use "nonclinical tests or studies", including non-animal models when scientifically appropriate. The significance of this change was both symbolic and practical. For decades, animal testing had been embedded in regulatory frameworks as the default expectation. By updating the statutory language, the FDA Modernization Act 2.0 formally acknowledged that scientific progress had expanded the toolkit available to developers. It signalled that human-relevant NAMs were not merely supplementary, but potentially sufficient in defined contexts.

However, the passage of the Act did not immediately trigger a widespread shift in industry practice. Several factors contributed to this measured response. First, while the legislation removed a legal requirement, it did not automatically establish detailed guidance on how and when alternatives would be accepted in place of animal data. Sponsors remained cautious, recognising that regulatory review ultimately depends on the totality of evidence and scientific justification. Second, broader adoption depends on experience and confidence in the performance of emerging platforms. As with any new scientific approach, organisations seek assurance that systems are robust, reliable and reproducible across studies and settings. Building that confidence requires well-characterised datasets, cross-laboratory experience and clarity around the context of use. Third, global harmonisation remained incomplete. Pharmaceutical development is inherently international and sponsors must consider requirements across multiple regulatory jurisdictions. Until broader alignment emerged, companies were hesitant to diverge dramatically from established global practices.

The next inflexion point came in April 2025, when the U.S. FDA announced a formal initiative to phase out animal testing requirements in specific areas over time, accompanied by a roadmap outlining how that transition would be achieved. Unlike the statutory revision in 2022, which simply removed an obligation, the 2025 announcement articulated and actively endorsed a new direction of travel. Crucially, the roadmap framed the transition as data-driven and iterative. Rather than setting arbitrary deadlines, it outlined measurable milestones, identifying priority areas where animal models are known to have limited predictive value, supporting comparative studies to benchmark NAM performance and increasing reviewer training to ensure consistent evaluation of alternative data streams. This approach acknowledged both the urgency of modernisation and the need for scientific rigour.

The FDA's announcement had an impact beyond U.S. borders. Regulatory science operates within a global ecosystem and leadership from one major agency often influences others. In

Date	Agency	Milestone & Impact
Dec 2020	FDA	ISTAND Programme Launch. Opens formal pathway for novel Drug Development Tools, such as Organ-Chips Chips.
Dec 29, 2022	US Congress	FDA Modernization Act 2.0. Removes statutory animal test test mandate; defines "nonclinical tests" to include *in vitro, in silico* and microphysiological systems.
Feb 6, 2024	US Congress	FDA Modernization Act 3.0 (introduced). Directs FDA to build a routine qualification pathway for NAMs.
Sep 24, 2024	FDA	First Organ-Chip accepted into ISTAND. Emulate's submission of the Liver Chip accepted into ISTAND. Emulate's submission of the LiverChip S1 for predicting DILI establishes Chip S1 for predicting DILI establishes evidentiary precedent.
Apr 10, 2025	FDA	Roadmap & Phase-Out Plan. Animal studies to become "the exception", prioritises MPS data and AI Out Plan. Animal studies to become "the exception", prioritises MPS data and AIdriven driven models.
Apr 29, 2025	NIH	Funding Priorities Shift. Grants now favour human-based technologies over animal-based technologies over animal-only studies.
May 29, 2025	US Navy	Ends Cat & Dog Experiments. Signals wider federal move toward NAMs.
Jul 7, 2025	NIH	Bars Animal-Only Proposals. Requires at least one validated human Only Proposals. Requires at least one validated human-relevant method in funded research.
November 11, 2025	UK Government	Announcement of a similar plan as the US FDA to phase out animal testing, with specific milestones and £75 million in new funding to help accomplish that goal.
January 22, 2026	US Environmental Protection Agency	Reaffirms its commitment to phasing out animal testing by 2035.
Early 2026	European Medicines Agency	The EMA is expected to issue guidelines on the reduction of animal usage in preclinical research in early 2026.

Table 1: A Timeline of Recent Regulatory Milestones

the months following the FDA's roadmap, other governments, including the United Kingdom, European Union and parts of Asia-Pacific, reiterated or expanded their own commitments to reducing reliance on animal testing. In the United Kingdom, policymakers highlighted NAMs within broader life sciences strategies and research funding priorities. In Europe and parts of Asia-Pacific, agencies signalled growing openness to incorporating advanced *in vitro* and computational methods into safety and efficacy assessments. A summary of major regulatory agency updates can be found in the table below.

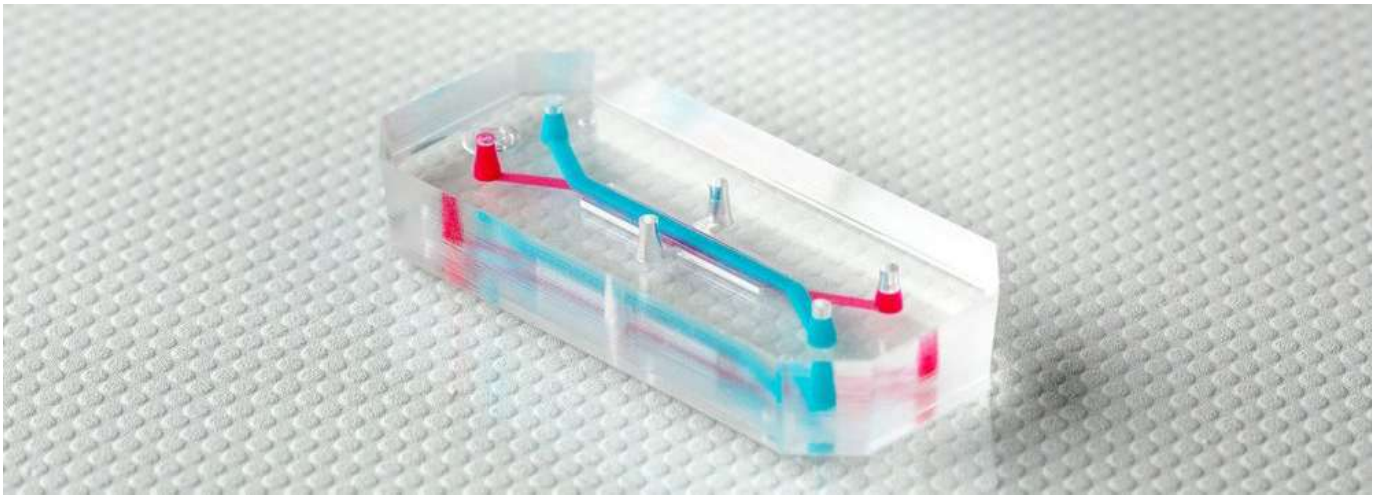
While the specific policies differ across jurisdictions, a clear pattern has emerged: regulatory authorities are no longer simply permitting alternatives; they are actively encouraging their development and structured integration. Importantly, though, none of these developments implies the immediate disappearance of animal models. Instead, these policies will foster a period of co-existence that will enable a gradual but deliberate rebalancing through incremental integration of NAMs, focusing first on where they address known limitations of existing models and where they can provide additional insight.

Organ-on-a-Chip Technology: Maturing to Meet Regulatory Demand

As regulatory expectations evolve, so too has the maturity of Organ-on-a-Chip technology itself. These systems were initially developed to capture key aspects of human tissue structure and function by combining primary or stem cell–derived human cells with microengineering (such as controlled fluid flow, shear stress and mechanical stretch), alongside *in vivo*-relevant factors such as a tissue-vascular interface and appropriate extracellular matrices. Early demonstrations focused on physiological credibility, reproducing barrier integrity, tissue–tissue interfaces, mechanical stretch or metabolic function in ways that conventional static culture could not. As the technology has developed, its value proposition has shifted accordingly, with [LE1.1]the emphasis increasingly on decision support; can results from a human-relevant microphysiological system influence a go/no-go determination, clarify a mechanistic ambiguity or strengthen a risk assessment? This reframing is essential for adoption within pharmaceutical organisations, where new methods must operate within established pipelines and development timelines.

As a decision-making tool, Organ-Chips are often introduced in areas where species differences are well recognised or where conventional models have shown limited predictive value. Human-specific toxicities that fail to manifest in standard preclinical species, mechanistic investigations requiring direct access to human tissue responses and de-risking programmes involving novel modalities or first-in-class targets are common entry points. In these settings, the goal is not wholesale replacement but enhanced confidence. By generating data in parallel with established *in vitro* and *in vivo* approaches, teams can assess concordance, explore discrepancies and build institutional familiarity without jeopardising regulatory-facing workflows.

As an example of how Organ-Chip data can enhance decision-making, consider recent work that evaluated a human Liver-Chip model in the context of drug-induced liver injury (DILI), one of the most common causes of clinical attrition and post-market drug withdrawals. In a study analysing nearly nine hundred Liver-Chips across 27 compounds with well–characterised clinical hepatotoxicity profiles, researchers benchmarked the performance of the Liver-Chip model against the historical behaviour of these drugs in humans and conventional preclinical



models.[1] The Liver-Chip correctly identified approximately 87% of compounds known to cause DILI in patients (despite passing through animal testing), with no false positives for non-hepatotoxic compounds, demonstrating both high sensitivity and specificity for the context of DILI prediction. These results suggest that Liver-Chips can outperform conventional preclinical approaches, offering earlier and more human-relevant indications of liver risk. By incorporating such data alongside animal and traditional *in vitro* models, teams can gain deeper mechanistic insight and more confidence in safety assessments earlier in development, ultimately reducing unnecessary downstream attrition and enhancing portfolio decision quality. This example highlights how Organ-Chip data, when aligned with defined contexts of use and performance benchmarks, can move beyond proof-of-concept toward practical integration in drug development strategies. Indeed, this Liver-Chip model is now in the final phase of the FDA's ISTAND program to qualify its use as a Drug Development Tool for the prediction of DILI in preclinical studies.[2]

This example also highlights a central theme in discussions of broader adoption of Organ-Chips and other NAMs, that of technological validation, of which there are multiple aspects to consider.

Technical robustness is, of course, one of the most important factors. Is the system reproducible within and across laboratories, stable over time and compatible with standardised analytical methods? Without consistent performance, even the most biologically compelling system will struggle to gain traction in risk-averse environments.

Equally important is clarity surrounding the context of use. Organ-Chip platforms are not designed to answer every preclinical question, nor should they be positioned as universal solutions. Their application should be appropriately defined around a specific objective, predicting a specific class of toxicities, interrogating a defined pathway or modelling a particular organ-level response, for example.

Comparative data will further strengthen confidence in the use of Organ-Chip data. Robust studies that evaluate Organ-Chip outputs alongside legacy animal data, established *in vitro* assays or known clinical outcomes will help stakeholders understand where these systems provide convergent insight and where they diverge. Notably, divergence is not inherently problematic; in some cases, differences illuminate the limitations of traditional models or reveal human-specific mechanisms that animal studies could not capture. Transparent reporting of both positive and negative results is essential to advancing collective understanding and value attribution.

Finally, regulatory engagement itself will also play a critical role in building confidence. Early dialogue around study design, endpoints and interpretation can clarify expectations and reduce uncertainty. As reviewers gain experience evaluating NAM-derived datasets, confidence will increase on both sides of the submission process.

Looking ahead, the role of Organ-on-a-Chip technology is likely to evolve in tandem with broader changes in regulatory science. If the past several years have marked the beginning of structural regulatory change, the coming years will test the industry's ability to convert that momentum into operational practice. The trajectory suggests not an overnight transformation, but rather a steady rebalancing, guided by human relevance, scientific rigour and a shared commitment to improving translational outcomes.

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