EXECUTIVE INSIGHTS

Advanced In Vitro Models: Opportunities and Challenges for US Drug Development

Advanced in vitro models are an emerging approach for preclinical experiments

Pharmaceutical companies invest over $50 billion annually in drug discovery and preclinical development, yet only 3% of drug candidates gain approval.[1] A significant portion of this spending goes toward experimental systems that are overly simplistic (e.g., 2D immortalized cell cultures), insufficiently predictive (e.g., rodent models) or ethically sensitive (e.g., nonhuman primate models), failing to fully replicate human pathophysiology and accurately predict both safety and efficacy of drug candidates.

Much of this testing is also driven by IND-enabling guidelines that rely heavily on animal-based data, reinforcing legacy models. As a result, biopharma companies must navigate the drug development process with suboptimal experimental tools that convey partial insight into biologic function/phenotype, leading to costly development cycles where many drug targets or candidates prove ineffective and fail later in development. These inefficiencies result in pharma companies allocating significant resources (e.g., time, money, labor) to projects unlikely to succeed.

Advanced in vitro models are an emerging class of tools that, alongside in silico modeling and artificial intelligence (AI) insights, are poised to unlock better decision-making regarding candidates earlier in the preclinical value chain.[2] Over the past few years, efforts like the FDA Modernization Act 2.0 and the ISTAND program have begun to ease regulatory barriers and encourage validation of nonanimal methods.[3,4] More recently, the FDA's announcement that it would phase out animal testing requirements for monoclonal antibodies (mAbs) marks a significant step forward.

Although this guidance remains relatively high level, it signals growing regulatory momentum toward broader acceptance of advanced in vitro models in drug development.[5] These advanced in vitro models aim to bridge the gap between simplistic 2D cell models (in vitro) and costly, low-throughput and ethically sensitive animal models (in vivo) by closely mimicking tissues or organ systems and providing predictive safety and efficacy data for critical systems (e.g., liver, kidney, heart).

Depending on eliminate application and intended placement in the value chain, advanced models have various archetypes, including organoids (or spheroids), organ-on-a-chip (OOC) systems and tissue-engineered organs (see Figure 1):

• **Organoids** are made of small clusters of primary or immortalized cells and, depending on the organ system, can contain multiple cell types. Certain cell types naturally self-assemble into macrostructures, allowing for more physiologically relevant properties compared to their 2D counterparts. Due to organoids' small size, ease of use and inexpensive design, they can be highly scaled (96-384 wells) and are lower cost compared to other advanced in vitro systems, allowing utilization earlier in the value chain for activities such as hit-to-lead screening.

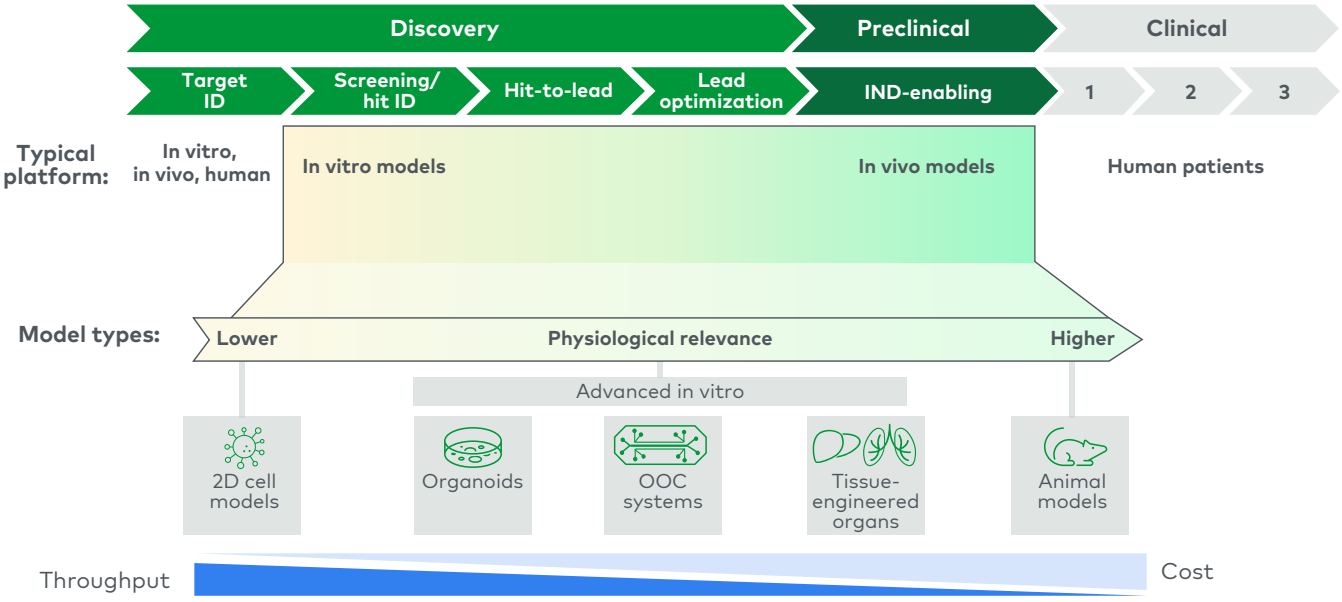
• **OOC** systems consist of microfluidic platforms seeded with organ-specific primary or immortalized cells (often multicellular with endothelial cells) and incorporate flow throughout the platform to mimic the body's vascular system, which may improve physiologic relevance. Their complex design and fabrication lead to higher costs and limited throughput (24- or 48-well formats), positioning them primarily in lead optimization.

• **Tissue-engineered organs** remain in an early stage of development and are primarily used in niche applications during later-stage optimization due to their complexity and cost.
These advanced in vitro systems have shown promising data that could improve decision-making and aim to improve each program's PTRS. For example, advanced liver organoids/chips have demonstrated the ability to produce physiologically relevant liver safety biomarkers (e.g., ALT, AST), and solid tumor organoids can replicate the tumor microenvironment to optimize therapeutic delivery and efficacy.

While applications for these technologies are extensive, they have historically faced significant headwinds to pharmaceutical adoption and widespread utilization. Many advanced in vitro tools have ended up stuck in the middle of legacy approaches, lacking the cost-effectiveness and throughput of 2D models as well as the validation and regulatory acceptance of animal models.

Figure 1

Advanced in vitro model utilization mapped across the discovery and preclinical value chain



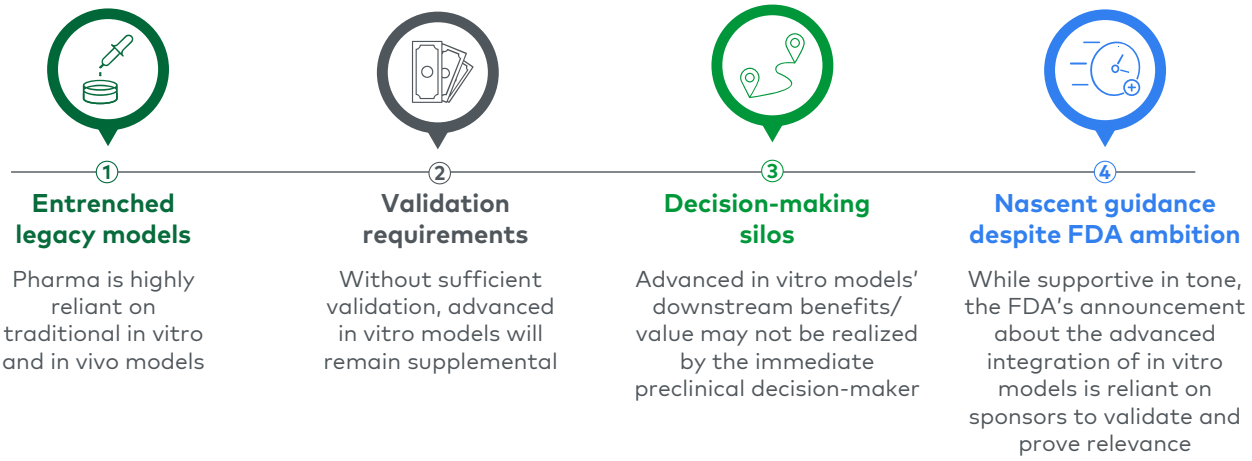
Note: ID=identification; IND=investigational new drug, OOC=organ-on-a-chip
Source: L.E.K. research and analysis

In this edition of *Executive Insights*, L.E.K. Consulting provides an overview of the headwinds impeding the adoption of these technologies and discusses some strategies to overcome these challenges.

Despite providing promising (albeit often incremental) human-relevant insights, advanced in vitro systems face a number of adoption headwinds as companies seek to expand the role these models play across both discovery and preclinical workflows. L.E.K. has identified four key challenges that must be addressed to unlock broader adoption and commercial impact for advanced in vitro tool suppliers (see Figure 2):

Figure 2

Key challenges faced by advanced in vitro tool suppliers



Note: FDA=Food and Drug Administration
Source: L.E.K. research and analysis

1. Current in vitro and in vivo models are highly entrenched within discovery and preclinical development workflows.

In vitro and in vivo models have long been foundational to pharmaceutical development, not because they are perfect but because they are trusted, are practical, and have consistently supported the discovery of clinically successful drugs. In vitro models typically consist of 2D cell models, and while these models are simplistic, pharma leverages them in high-throughput formats (384-well plates) in single-readout assays to assess efficacy or safety across large compound libraries. Often these 2D cell model assays recapitulate a disease state (e.g., breast cancer) or test a safety attribute (e.g., hERG ion channel safety). Although advanced in vitro models may offer greater accuracy, the acceptance, entrenchment and throughput of 2D models create a high barrier to adoption.

Additionally, the higher cost of these advanced in vitro systems may not be justified by their performance benefits, making practicality a key consideration. Recently, suppliers have focused on complex disease areas that lack a simple 2D model (e.g., I/O or muscular dystrophy) and where advanced models support a higher throughput not previously possible. Suppliers are increasingly integrating AI with advanced models to drive throughput and extract insights about disease mechanisms. AI and machine learning (ML) algorithms can help simplify complex data and identify early patterns of efficacy and toxicity.

In vivo rodent models are typically used starting in lead optimization to evaluate candidates in physiologically relevant systems. These models are leveraged for a suite of experiments (e.g., safety, efficacy and ADME studies), often with multiple readouts from a single animal.

For example, dose escalation studies will also enable toxicity and pathological assessment of organs (e.g., liver, kidney, heart).

While advanced in vitro models may be as predictive as in vivo models, their lack of physiological complexity/context (e.g., multi-organ systems) limits widespread utilization and has kept many researchers from replacing in vivo models. Animal models that are resource-intensive or offer limited translational value (e.g., nonhuman primates) are increasingly viewed as entry points for advanced in vitro approaches, and recently, suppliers have been targeting use cases where large numbers of animals are utilized for only a single specific readout (e.g., gene therapy, titer optimization).

Suppliers are using AI/ML in combination with these systems to further help researchers model vector performance, predict optimal capsid design and understand transduction efficiency. Beyond gene therapy, AI and advanced systems are helping reduce animal use across complex and poorly predicted areas, such as cardiac toxicity and immune response, demonstrating that advanced systems may serve as a strong starting point toward supporting the FDA's goal of reducing and eventually eliminating animal testing.

2. Advanced in vitro systems are likely a supplemental cost until fully validated.
Validation is key to convincing stakeholders to choose an advanced in vitro model over the current gold standard; however, it remains a moving target. Without sufficient validation, researchers must still conduct legacy experiments, making advanced in vitro models a supplemental cost rather than a replacement. Stakeholders often require both retrospective and prospective validation. For retrospective validation, suppliers leverage therapeutics with known toxicity profiles to show that advanced in vitro models can predict similar specificity and sensitivity. Some models have shown toxicity from therapeutics that failed clinical trials but were not deemed toxic using traditional in vitro and in vivo models.

Pharmaceutical stakeholders also seek prospective validation, where other researchers successfully use this advanced in vitro tool to support a drug's progression to clinical trials and potentially eventual approval. Taken together, retrospective and prospective validation are costly, as they require high upfront investments and initial adoption by multiple champions. In today's cost-constrained and time-sensitive environment, studies are often hard to justify, particularly when they do not replace existing experiments. Justifying these extra costs remains a headwind for suppliers, and without broad validation, advanced in vitro models are likely to remain additive to development workflows.

To overcome this, suppliers must sharpen their value proposition to attract champions and clearly demonstrate practical utility. A growing number of suppliers are leveraging AI/ML to validate and benchmark their models against known clinical outcomes to enhance regulatory credibility and commercial adoption. AI/ML algorithms can analyze high-dimensional data (e.g., transcriptomics, phenotypic screens) to demonstrate that in vitro models align with relevant disease biology and drug response. The FDA's most recent guidance may accelerate broader collaboration across advanced in vitro approaches to build confidence and momentum.

3. Advanced in vitro model value accrues downstream and may go unrecognized by purchasing stakeholders

Discovery and preclinical teams are often siloed from their clinical counterparts, hindering the realization of advanced in vitro models' full value. This disconnect means the buying team may not recognize downstream benefits, such as improved PTRS, from better early-stage decisions. For example, if an organoid model helps discovery scientists eliminate candidates with hepatotoxic profiles, the benefit of delivering a lead candidate with a lower risk of liver damage to preclinical studies or clinical trials may go unnoticed.

This lack of cross-team visibility also applies to cost and time savings, as preclinical and clinical teams may not fully recognize the impact of early discovery failures. These efficiency gains and cost savings can be overlooked when transitioning candidates across stages of the value chain. Additionally, "kill quickly" is not always incentivized, as many researchers are evaluated based on the number of candidates, not necessarily the success of those candidates downstream.

To demonstrate value, advanced in vitro model suppliers must track how their tools have supported key decision points (e.g., deprioritizing candidates based on early safety or efficacy signals) and highlight the productivity gains (e.g., longer and more costly in vivo studies). This task can be difficult, as each clinical asset likely passes through multiple models and hundreds of experiments, and each advanced in vitro model must lean on its value proposition to convince the pharma industry of its impact.

4. The FDA's recent announcement signals progress, but broad replacement of animal models will be a cautious and slow process.

Despite the growing evidence supporting advanced in vitro models over traditional in vitro and in vivo testing, the FDA has been slow to fully embrace these technologies and integrate them into regulatory frameworks. While the agency has taken incremental steps in recent years, such as issuing guidance documents, supporting legislation (e.g., FDA Modernization Act 2.0), launching qualification programs (e.g., ISTAND) and supporting collaborative research, the pace of adoption remains cautious.

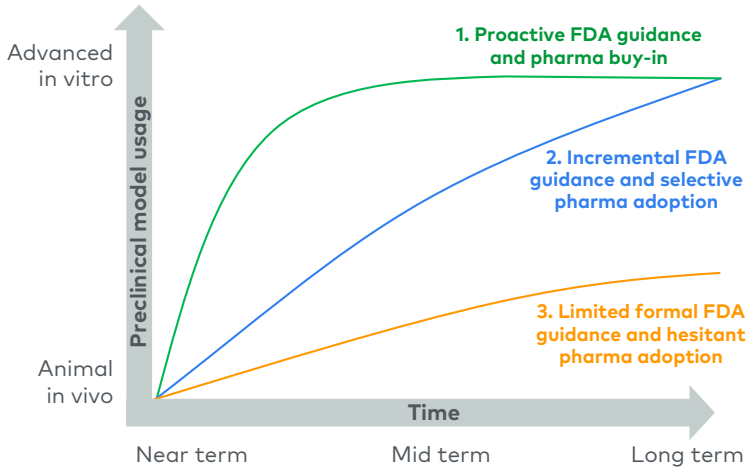
The most recent FDA guidance indicates a more active stance on reducing animal usage and relying on alternative models. However, beyond the reduction of primate study requirements for mAbs, the roadmap remains aspirational. Outside select, more mature applications (e.g., liver OOC), the advanced in vitro space is nascent, with many emerging models lacking validation and the confidence of sponsors. The FDA highlights early-stage concepts, such as whole-body-on-a-chip systems and AI/ML models for pharmacokinetics, but provides limited clarity on regulatory expectations or actionable pathways for adoption.

While the FDA's tone is supportive of a transition to more predictive tools, for now the burden of validation and regulatory evidence falls to pharma sponsors, which must determine whether the FDA is truly accepting of data from organoids or OOC systems. Additionally, the FDA and the pharma industry must account for other stakeholders such as clinical teams that may be hesitant to recruit for studies built on unfamiliar toxicology data.

Still, this guidance marks an important inflection point. Depending on how industry and regulators act in the near, mid- and long term, adoption could accelerate meaningfully or continue at a slower pace (see Figure 3). Pharma will play a critical role in generating the validation data needed to shift regulatory perception, especially in high-priority use cases where existing models are costly or poorly predictive. If adoption is effectively executed with coordinated validation, clearer expectations and support across advanced in vitro, in silico and AI/ML models, this recent guidance could drive broader adoption efforts across pharma company silos and organizations, offering meaningful tailwinds for suppliers if these efforts translate into real change.

Figure 3

Future advanced in vitro model adoption scenarios following the recent FDA announcement



1
- **FDA builds momentum** with clear guidelines and defined, efficient validation pathways
- **Pharma begins parallel validation** at scale
- **AI tools help generate supportive evidence** quickly

2
- **FDA supports advanced in vitro systems on a case-by-case** basis, without clear guidance
- Adoption and validation are focused on **high-burden or less-predictive use cases** in discovery and preclinical stages

3
- FDA supports advanced in vitro systems in tone only with **limited formal guidance** or qualification pathways
- **Validation costs remain high,** with pharma hesitant to adopt without regulatory clarity

Note: FDA=Food and Drug Administration
Source: L.E.K. research and analysis

To cultivate the adoption and impact of advanced in vitro models, both suppliers and users should consider several key success factors. Given these challenges, how can an advanced in vitro model supplier accelerate adoption and find success within this market? And with the FDA's recent announcement, how can pharma stakeholders drive meaningful efficiency and return on investment by integrating these models into the drug development process?

- **Pursue a more targeted approach and sharpened value proposition.** Suppliers must deeply understand the disease areas and use cases (e.g., safety vs. efficacy) where there is sufficient unmet need or market pain to overcome adoption barriers. This includes clearly defining where their technology fits within the drug development value chain (e.g., target identification, drug screening, candidate selection, lead optimization or clinical trial support). At the same time, pharma should actively assess where advanced in vitro systems can be introduced to add value, particularly in these high-cost, less-predictive areas, as an initial step toward broader integration.
- **Strategically build the necessary data sets to validate the value proposition.** Based on the key use cases, suppliers must identify the key pieces of evidence necessary to demonstrate how their solutions complement (e.g., addressing safety concerns) or replace (e.g., outperforming HTS on efficacy) current models or eliminate existing bottlenecks so that pharmaceutical companies can confidently integrate these systems into their workflow. Recent FDA guidance may begin to define a clearer path toward recognizing these models

as primary models, rather than supplemental tools, within drug development workflows. The pharma stakeholders should look to partner in this effort by generating or supporting validation in parallel with legacy tools, especially in their high-priority use cases.

- **Establish a clear deployment/business model (e.g., product, service or hybrid approach).** Suppliers must clearly define what is included in their offering — from core technologies to ancillary services such as data analysis, regulatory support and validation studies — and tailor their model to reduce adoption barriers for customers unfamiliar with advanced in vitro systems while clearly demonstrating the solution's value proposition. Pharma should seek supplier support to implement these models effectively within their existing R&D frameworks as the FDA transitions from animal models.

By refining their approach and aligning with industry needs, advanced in vitro model suppliers can overcome adoption barriers and demonstrate their value more effectively. Pharma should also prepare for a future where these models play a larger role, by identifying areas of fit and building internal readiness for adoption.

To explore how L.E.K. can help you navigate the opportunities and challenges in the advanced in vitro market, please reach out to our team. We can offer strategic guidance to set you up for success in this evolving space.

For more information, please **contact us**.

Endnotes

[1]LEK.com, "The Financial Ecosystem of Pharmaceutical R&D." https://www.lek.com/insights/sr/financial-ecosystem-pharmaceutical-rd

[2]LEK.com, "New Drug Discovery Paradigm: Advances in 3D Tissue Models and Applications." https://www.lek.com/insights/ei/new-drug-discovery-paradigm-advances-3d-tissue-models-and-applications

[3]Congress.gov, "S.5002 - FDA Modernization Act 2.0." https://www.congress.gov/bill/117th-congress/senate-bill/5002

[4]FDA.gov, "Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program." https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/innovative-science-and-technology-approaches-new-drugs-istand-pilot-program

[5]FDA.com, "FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs." https://www.fda.gov/news-events/press-announcements/fda-announces-plan-phase-out-animal-testing-requirement-monoclonal-antibodies-and-other-drugs

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