Bridging the ADMET Translational Gap:
How New Approach Methodologies and Organ-on-a-Chip Technology Are Redefining Drug Development

Drug developers face challenges in translating preclinical findings to safe and effective human trials. Traditionally, preclinical testing relies on a phased approach that combines simple *in vitro* assays and whole animal *in vivo* studies; however, a translational gap remains between these findings and the clinical outcomes.

The translational gap is caused by the limited ability of simple *in vitro* assays to accurately predict human responses, combined with the interspecies limitations of animal studies, a core requirement by global regulatory bodies before human trials, unless no suitable model exists. The transition from preclinical models to human subjects therefore requires navigating complex pharmacokinetic (PK) and toxicology uncertainties that vary significantly by drug modality and therapeutic area.

Our inability to adequately address these uncertainties is represented by consistently high drug attrition rates. Toxicity remains one of the most significant causes of drug attrition, accounting for 30% of drug failures in the clinic.[1] Poor human translation in pre-clinical PK studies is also a major driver of clinical failures, with PK and bioavailability listed as the third most common cause of attrition and 16% of all failures.[2]

The relatively poor predictability of animal models, alongside a pull for more ethical and sustainable science, has led to recent regulatory shifts from the US FDA and the UK Government, highlighting their respective commitments to phasing out animal testing in favour of animal alternatives, known as New Approach Methodologies (NAMs).

We now stand at a pivotal moment in drug development, with regulators signalling a future where NAMs, such as *in silico* models and microphysiological systems (MPS), are more than just peripheral tools; they will now become central to defining how new medicines are discovered, evaluated and approved. To facilitate broader adoption and expedite the pace of change, numerous efforts are being deployed to validate and standardise NAMs for use in regulatory submissions, with many drug developers already using a broad range of NAMs for internal decision making.

This article will explore how NAMs can be utilised in combination to predict a translatable first-in-human dose to support earlier pipeline decision-making and enable developers to build greater confidence in their lead candidates.

Why Is There Momentum Behind NAMs' use to Bridge the ADMET Translational Gap?

In 2025, the FDA announced its decision to phase out animal testing requirements for monoclonal antibodies, followed by other drugs, signalling a clear shift towards the use of more relevant human approaches for preclinical safety and toxicity testing. Later in the year, the UK government announced its plans to phase out animal testing faster, where reliable and effective alternative methods can replace them by offering the same level of safety for human exposure. Specifically called out was a goal to reduce pharmacokinetic studies using dogs and non-human primates by 2030.

Another clear window into the inevitability of NAMs moving from promise to regulatory reality can be found by looking at the FDA's Innovative Science and Technology Approaches for New Drugs (ISTAND) Programme. While the sample size is modest, the dataset reveals patterns about regulatory expectations, timelines and which technologies are most likely to succeed. As of the 21st January 2026, six of 15 accepted technologies being evaluated in the Drug Development Tool database are MPS, a type of Organ-on-a-chip technology for toxicity testing and drug dosing.

Alongside regulatory announcements, partnerships between MPS providers and the industry's support network of CROs further demonstrate the growing acceptance of MPS platforms as strategic tools that address real-world translational gaps and enable better preparedness for the clinic. From our experience, most contract research studies are currently focused on the use of MPS to solve late-stage challenges, such as exploring dose setting for drugs with a narrow therapeutic window or seeking clarity where there is conflicting data from preclinical species. However, the real efficiency and benefits of MPS come from integrating the technology earlier to guide decision making rather than troubleshooting. As more companies see how MPS helps bridge the translatability gap, adoption is likely to shift increasingly toward earlier stages.

The power of NAMs to change how lead candidates are selected is something that will be led by their use as a collective, rather than in isolation. For example, data generated by MPS becomes far more insightful when combined with *in silico* tools, such as physiologically based pharmacokinetic (PBPK) models, machine learning and computational toxicology frameworks to bridge gaps between *in vitro* findings and predicted human responses.

The Limitations of Standard *In Vitro* DMPK Tools

Caco-2 epithelial cells have long been heralded as the gold standard for studying intestinal absorption and permeability. However, these immortalised colorectal adenocarcinoma cells have well-documented limitations in fully replicating the complexity of the human intestine. Notably, expression of key enzymes involved in the hydrolysis of ester prodrugs is neither physiological nor human-relevant in Caco-2 cells, affecting the accurate prediction of the metabolism and absorption of ester-containing drugs. Furthermore, this model operates in isolation and therefore cannot profile the contribution to bioavailability of both the gut and liver. Because of these shortcomings, Caco-2 assays often necessitate additional

animal studies, which would not have been required had more advanced and appropriate models been used.

Enabling Human-Relevant Insights for Bioavailability and Oral PK Profiling Using MPS

A critical differentiator of MPS is the ability to measure and model drug exposure within the tissue environment. Unlike static cultures, MPS incorporate perfusion, microfluidics and multi organ communication, all of which influence drug distribution. For regulatory submissions, simply stating the nominal concentration added to the medium is insufficient. Researchers must be able to articulate what exposure the tissues experienced over time and whether clinically relevant maximum concentration, area under curve, or steady-state levels were achieved.

Establishing pharmacokinetic/pharmacodynamic (PK/PD) relationships within MPS assays is essential for demonstrating translational validity. It allows regulators to understand not just what happened in the system, but why it happened and how it relates to human dosing. Moreover, this alignment strengthens the case for reducing animal studies where discrepancies in absorption, metabolism or clearance can obscure human-relevant outcomes.

There are examples of MPS approaches that address these challenges, including a Gut/Liver MPS described by Abbas et al. in 2025, comprising entirely primary human gut and liver tissues capable of data-rich insights into both oral and intravenous drug dosing.[4] The system recapitulates two critical determinants of human PK, intestinal permeability and first-pass metabolism. By linking gut and liver tissues under perfusion to mimic blood flow, the model replicates the sequence of drug absorption and metabolism, enabling mechanistic insights with significantly more accuracy than animal models or conventional static cultures.

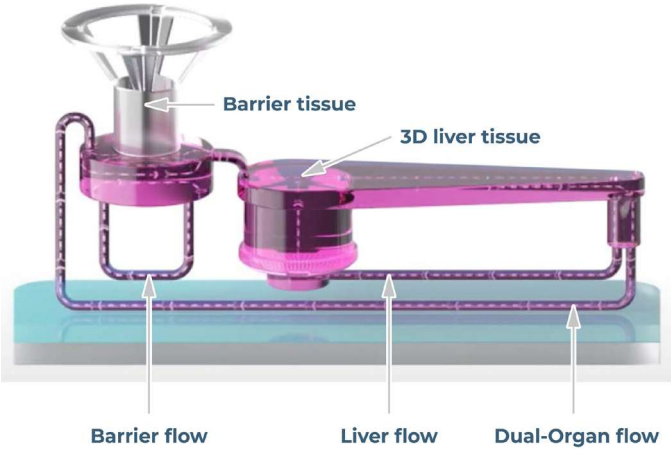

Figure 1. A schematic diagram of one well of a Dual-organ Multi-chip plate, demonstrating how MPS incorporates perfusion to replicate the sequence of drug absorption and metabolism.

The study also demonstrated how data derived from the Gut/Liver MPS-based bioavailability assay can be quantitatively integrated with *in silico* computational modelling, enabling the prediction of tissue-specific PK parameters, generating robust and reliable data to close the translational gap and enabling an improved estimation of preclinical bioavailability. Understanding oral bioavailability is particularly crucial as it shapes dose predictions, therapeutic efficacy expectations, safety margins and formulation strategies.

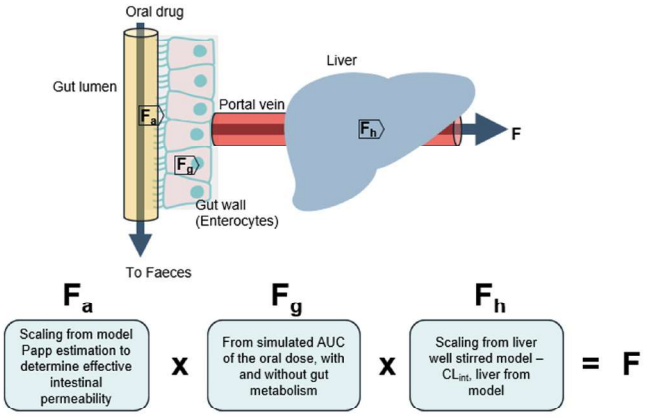

Figure 2. Combining data derived from a Gut/Liver MPS with a mechanistic mathematical model accurately predicts key ADME parameters and oral bioavailability by estimating the fraction absorbed (F_a), the fraction escaping gut metabolism (Fg) and the fraction escaping hepatic metabolism (F_h).

The Limitations of Standard Liver Safety Tools

Liver toxicity remains one of the most significant causes of drug attrition, accounting for 18% of drug development failures due to adverse reactions.[5] Existing methods to assess liver toxicity are poorly suited to predicting results in humans. Both standard 2D and simple 3D cell cultures lack the complexity and longevity to predict or understand the mechanism of complex or latent events, whilst animal models can inaccurately reflect human outcomes due to differences in genetics, metabolism and immunological responses. As a result, unsafe drug candidates may progress too far, and potentially life-saving ones may be misclassified and abandoned.

Advancing Liver Safety and DILI Assessment with MPS

Liver MPS (or Liver-on-a-chip) are essentially co-cultures of primary human cells, including hepatocytes and Kupffer cells, which are crucial for maintaining liver function and detecting inflammatory responses.[6] They are cultured under perfusion to simulate the liver microenvironment, including blood flow and mechanical shear stress. Perfusion is essential for promoting high metabolic activity, culture longevity (for repeat dosing studies) and liver-specific biomarker detection, including albumin and ALT/AST, for enhanced data translatability. Earlier and more advanced assessment of human liver toxicity using MPS enables promising drugs to undergo structural modifications and move forward with more confidence or caution.

It is important to note that not all MPS offer the same degree of data output for mechanistic insights, sensitivity for predicting complex toxicities such as cholestasis or longevity.[7,3] Thus, an understanding of which platforms are better suited to the different stages of drug discovery and development is required. The most advanced *in vitro* tools enable the sensitive evaluation of compound toxicity with full dose-response curves and deep mechanistic insights that go beyond intrinsic DILI predictions.[3,5–9] Advanced MPS models capture a wide spectrum of biological signals, from simple cell health markers to complex multiomics datasets. The key to their successful implementation is to align endpoints with the biological questions and anticipated clinical context. For example, when assessing hepatotoxicity, combining functional outputs (albumin secretion), structural changes (histology or imaging) and mechanistic biomarkers (stress pathways, metabolic flux) provides a multidimensional view of drug response that is far more compelling to regulators than any

single readout. By understanding the mechanism behind the cause, MPS provides the foresight into potential DILI liabilities that can be subsequently managed via more informed risk mitigation strategies.

In addition to predicting human Drug-induced liver injury, Liver MPS can also be used to predict interspecies differences before *in vivo* testing or address discrepancies between traditional human *in vitro* methods and *in vivo* animal studies that make it challenging to predict safety risks during preclinical testing. In these scenarios, cross-species MPS models further expand the *in vitro* to *in vivo* extrapolation (IVIVE) capabilities of MPS-based assays by offering rapid, comparative studies of human and animal responses.[10]

MPS & *In Silico* Approaches as a Cornerstone of Future Drug Development

MPS are no longer experimental curiosities or ethical alternatives; they are a regulatory-endorsed approach with research demonstrating scientific superiority in generating truly translational human-relevant data. When thoughtfully designed, rigorously executed and integrated with computational approaches, MPS assays provide compelling evidence to support regulatory submissions and, in some cases, fill critical gaps left by traditional animal models.

Embracing NAMs, including MPS technologies, offers a strategic advantage for ADME and toxicity studies when utilised in combination to predict a translatable first-in-human dose that balances tolerability versus optimal pharmacokinetic profile. Going forward, the earlier use of NAMs will support earlier pipeline decision-making, greater confidence in lead candidates, mechanistically informed regulatory packages, the transition away from animal testing and accelerate the path to market.

The strategic use of MPS platforms will increasingly define the scientific backbone of future drug development. For researchers across the biotech and pharmaceutical sectors, now is the time to invest in the frameworks, skills and partnerships needed to run MPS assays with the level of rigour regulators expect. Those who do will be well positioned to accelerate innovation and bring safer, more effective medicines to patients faster and with science that truly reflects human biology.

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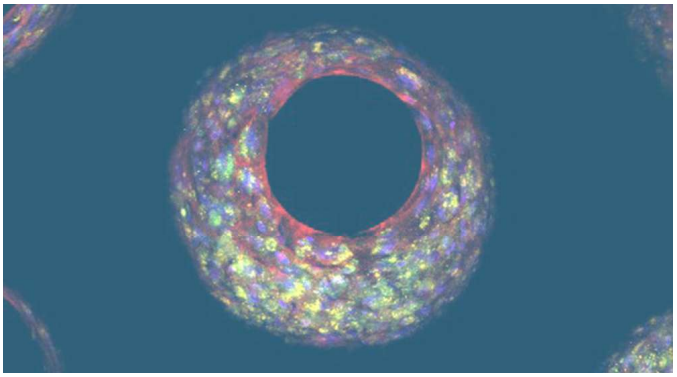

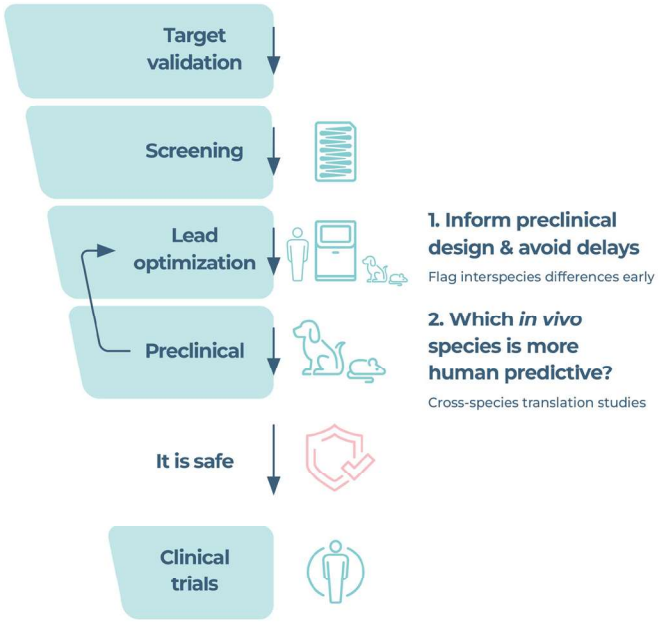

Figure 3. The drug discovery and development stages where human and cross-species Liver MPS advance liver safety and DILI assessments

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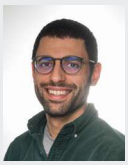

Dr. Yassen Abbas

Dr. Yassen Abbas is Biology Group Leader at CN Bio, leading a team advancing organ on a chip applications in ADME and oral bioavailability, digital twins, and CAR T therapy models. His background includes the European Space Agency, a PhD and postdoc at the University of Cambridge in tissue engineered models of human reproduction. He has authored peer reviewed publications, including six first author papers, and is named on three patent applications.