CN-BIO

2026 WEBINAR SERIES

# Addressing Unmet DILI Challenges: Novel insights from adaptable Liver microphysiological systems

**A full run down of questions & answers from our March 3rd webinar**

# Glossary

**ADME –** Absorption, Distribution, Metabolism and Excretion. A collective term describing the pharmacokinetic processes that determine the exposure of a drug within the body.

**COC (Cyclic Olefin Copolymer) –** A low binding plastic material used in PhysioMimix consumable plates to minimise non specific compound adsorption, particularly for hydrophobic or adsorption prone drugs.

**CRS (Contract Research Services) –** CN Bio services offering experimental design, execution, and data analysis using PhysioMimix platforms for customers who prefer to outsource studies.

**DILI (Drug Induced Liver Injury) –** Liver damage caused by exposure to drugs or their metabolites; a leading cause of clinical trial attrition and post market drug withdrawal.

**FDA (U.S. Food and Drug Administration) –** The U.S. regulatory agency responsible for protecting public health through regulation of drugs, biologics, and medical devices.

**IND (Investigational New Drug) –** A regulatory submission to the FDA requesting authorisation to begin clinical trials in humans.

**IND enabling –** Refers to studies conducted to support an IND submission, including safety, pharmacology, and translational assessments.

***In silico* –** Computer based or computational modelling approaches used to simulate or predict biological processes.

***In vitro* –** Experiments conducted outside a living organism, typically in a laboratory setting using cells or tissues.

***In vivo* –** Experiments conducted within a living organism.

**MASH (Metabolic Dysfunction Associated Steatohepatitis) –** A chronic liver disease characterised by steatosis, inflammation, and fibrosis associated with metabolic dysfunction.

**MPS (Microphysiological System) –** An advanced in vitro model that recreates aspects of human organ structure and function using human cells under controlled, dynamic conditions; also referred to as Organ on a Chip systems.

**NAMs (New Approach Methodologies) –** Innovative non animal methods, including MPS, computational modelling, and advanced in vitro assays, used to assess drug safety and efficacy.

**OOC (Organ on a Chip) –** A class of microengineered systems designed to mimic the physiological function of human organs; often used interchangeably with MPS in this document.

**PBMCs (Peripheral Blood Mononuclear Cells) –** Immune cells isolated from blood, including lymphocytes and monocytes, commonly used to study immune mediated mechanisms.

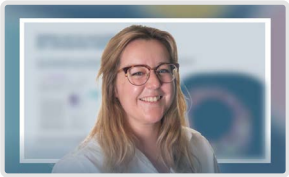
**PDMS (Polydimethylsiloxane) –** A silicone based elastomer commonly used in microfluidic devices; known to absorb small molecules and therefore avoided in PhysioMimix consumables.

**Pre IND –** The stage of drug development prior to IND submission, typically encompassing late discovery and lead optimisation.

**µL (Microlitre) –** A unit of volume equal to one millionth of a litre.

**µL/s (Microlitres per second) –** A unit of flow rate used to define intra and inter organ

# Q&A participants



**Dr. Emily Richardson**

Biology Group Leader, CN Bio

## Watch webinar

If you missed our live webinar you can watch it **on-demand here**

## Another question?

Drop an email to one of our experts
**sales@cn-bio.com**

# Questions

Q1

**How do you see MPS models evolving to better capture systemic events that single organ models can't currently capture?**

While this presentation mainly focuses on our Liver microphysiological system (MPS), it's important to recognise that the field is rapidly expanding beyond single-organ models. Both CN Bio and the wider MPS community are actively developing additional organ models, which opens the door to more integrated and physiologically relevant approaches.

Looking ahead, I see the field moving increasingly toward combinational and multi-organ strategies, where multiple MPS or new approach methodologies (NAMs) are linked together to better capture systemic effects that cannot be reproduced in isolation. As these systems become more complex, their predictive power will be further enhanced by integrating experimental data with *in silico* and computational modeling, allowing us to interpret inter-organ interactions more holistically.

At CN Bio, we have already begun this journey. Our PhysioMimix® **drug bioavailability assay** fluidically links a human Gut and Liver MPS, enabling the simultaneous study of intestinal absorption and hepatic metabolism. In parallel, we have developed computational models that build on these experimental data to predict human bioavailability more accurately.

To learn how combining MPS with *in silico* modelling enhances oral bioavailability predictions, watch this webinar on demand: **MPS and In Silico Modeling: The next generation of bioavailability prediction**

Together, these integrated *in vitro* and *in silico* approaches represent an important step forward for modelling systemic biology and will be increasingly critical for improving human relevance in drug development decision-making.

---

Q2

**To what extent are regulatory bodies currently accepting microphysiological system (MPS) and Organ-on-a-chip (OOC) data?**

As I mentioned earlier in the presentation, CN Bio has been

actively involved in regulatory-facing initiatives for several years, contributing to the broader evaluation of MPS by regulatory agencies.

Our engagement with regulators, particularly the U.S. Food and Drug Administration (FDA), began around 2019 and has been a long-standing and strategic effort, and has resulted in the publication of the first regulatory and MPS provider collaborated publication: *Characterizing the Reproducibility in Using a Liver Microphysiological System for Assaying Drug Toxicity, Metabolism and Accumulation*, ***Rubiano et al (2021)***

More broadly, there has been a notable acceleration in regulatory momentum over the past few years. Developments such as the **FDA Modernization Act 2.0**, the **FDA 2025 roadmap to reducing animal testing**, the publication of the **UK roadmap for the reduction of animal testing**, and the anticipated European Commission's roadmap - all signal strong regulatory alignment around the adoption of NAMs, including MPS to reduce unnecessary animal use. Regulators are clearly engaged, and there are now ongoing, open discussions across multiple regions about how and where these models can be applied most effectively.

In terms of real-world usage, MPS data is already being incorporated into regulatory submissions. Data generated by CN Bio's Contract Research Services (CRS) team supported filing of **Inipharm's INI-822 for metabolic liver disease treatment**, with other applications currently in progress. While this activity does not always take place in the public domain, it demonstrates that MPS data is not only being evaluated but actively used to support regulatory decision-making.

Overall, I strongly believe this is a critical moment for the field. Generating robust, high-quality MPS data and engaging early with regulators to demonstrate its relevance is essential. Now is the time to integrate these models into development pipelines and to showcase their value in a regulatory context.

---

Q3

**How long do you think Animal MPS will be useful for? Are they a short-term solution or do they have a long-term use case?**

Animal MPS can be viewed as an important bridging tool rather than a replacement technology. Their primary value lies in helping researchers build greater confidence in how MPS data translates across species and, ultimately, to humans.

One particularly valuable application is in situations where

conflicting animal data are observed during development. For example, when a compound shows a positive signal in one species, such as rat, but not in another, such as dog, animal MPS can be used alongside human MPS to interrogate those differences in a controlled, mechanistic way. This enables researchers to understand whether an observed finding is driven by species-specific biology or is likely to be relevant to humans.

Running animal and human MPS in parallel allows for deeper investigation into the underlying mechanisms responsible for divergent outcomes. This approach can support more informed decision-making by clarifying whether a potential safety finding represents a genuine human risk or reflects a species-specific effect. As highlighted in the publication, ***Negi et al. (2025)***, this kind of mechanistic insight is critical when interpreting discordant *in vivo results*.

Another possible use for cross-species MPS is within lead optimization to flag interspecies differences early or proceed with confidence. Here animal MPS can potentially reduce the number of animals used in safety studies – for example, candidate drugs could be first screened in animal MPS to reduce risks of potentially toxic drugs going through to *in vivo* testing, determine dose ranges or regimens, or analyse the species suitability for testing - whilst also mitigating the risk of late-stage conflicting data. Here our Multi-chip Liver-48 plates provide the throughput required for this drug discovery phase with up to 288 samples per run capacity.

That said, this is still an evolving area, and it remains too early to draw definitive conclusions about how animal MPS will be adopted more broadly. It will be interesting to see how the field develops, and continued dialogue from the community will be essential as best practices emerge.

---

Q4

**Can we use machine learning and deep learning algorithms in drug-induced liver injury (DILI) to predict it early?**

There are some highly credible efforts underway to apply machine-learning approaches to existing preclinical and clinical datasets, and the progress in this space is extremely encouraging.

In particular, machine learning and *in silico* tools can play a valuable role as early-stage screening approaches, helping to prioritise compounds, identify potential risks, and guide experimental strategy before more complex or resource-intensive studies are undertaken. When used in this way, these tools can significantly

improve efficiency and decision-making.

Looking ahead, I strongly believe that the future lies in combining machine learning, *in silico* modeling, and experimentally derived data from MPS. Each approach brings complementary strengths, therefore, an integrated strategy has the potential to deliver more predictive insights across the drug development pipeline.

---

Q5

**Where in DILI assessments do MPS provide the most benefit above other *in vitro* models like spheroids?**

In the webinar, we demonstrated how our Liver MPS and DILI assay provides far more mechanistic-based information than a simple yes-or-no readout. We are not relying solely on cell death or loss of viability as an endpoint, nor are we asking whether cells are simply functional up to a certain exposure and non-functional beyond that. Instead, Liver MPS enable us to interrogate biological responses well before overt toxicity occurs. This includes monitoring changes in cellular function, stress responses, and mechanistic signals that emerge at sub-toxic concentrations. By capturing these earlier and more nuanced events from a single Liver-chip, we can build a much deeper understanding of how and why a compound is exerting its effects.

This depth of insight is where MPS are particularly powerful. They allow us to adopt a more scientifically rigorous, mechanistic approach to evaluating risk; making MPS a valuable tool for addressing complex safety and translational questions.

To learn how you can capture more complex mechanisms of human DILI using PhysioMimix, read this application note: **Evaluating a human DILI assay's ability to unlock complex mechanisms of toxicity**.

---

Q6

**Where do you see Liver MPS adding the most value in the drug development pipeline?**

In my opinion, MPS deliver the greatest value when used in the late-discovery/ pre-investigational new drug (pre-IND) window; i.e. just prior to initiating *in vivo* studies.

Once lead candidates have been selected and teams are preparing to move toward IND-enabling work, there is a critical need to understand the human relevance of signals observed in earlier *in vitro* models before committing significant time, cost, and resources downstream.

This point in the drug development process represents a real turning point. Go/no go decisions made at this stage of the pipeline - around candidate progression, study design, and risk tolerance, all have a disproportionate impact on development success.

MPS offer a unique opportunity to interrogate biological responses in a more human-relevant and mechanistic way, helping teams better understand whether observations seen in traditional *in vitro* systems are likely to translate meaningfully *in vivo*.

Q7

**What is your opinion on single versus pooled donors for daily testing?**

At CN Bio, we have tested both pooled and single donors in the past; however, our preference is to use single donors.

Firstly, this approach allows us to understand donor-specific responses, rather than averaging effects across a pooled population.

Secondly, when donor cells are pooled together, we often do not retain the same population by the end of an experiment. Some donor cells may survive or function better than others over the course of the study, which can alter the final outcome; making it more challenging to meaningfully interpret the data.

For toxicity studies in particular, our preference is to use single donors. Using the **PhysioMimix Core System**, we can test multiple individual donors alongside each other, enabling the identification and comparison of donor-specific responses.

Q8

**Can I use my own donors for PhysioMimix, DILI experiments?**

Yes, absolutely. This is commonly done by PhysioMimix Core users.

Many researchers have very specific questions they are trying to answer—for example, understanding how a particular disease phenotype, genetic background, or clinical history influences drug response. In those cases, it makes complete sense to work with donors that are directly relevant to the biology or patient population of interest. The PhysioMimix platform is open and adaptable, fully supporting that approach.

Our blog “Mirror, mirror on the wall which is the best cell of them all?” explores how to validate your choice of donor cells for MPS studies

We also **validate and qualify donors** for use in the System, which can be particularly helpful for teams that are new to MPS. Starting with a donor that we already have extensive experience with helps ensure a smooth onboarding process and experimental success, before moving on to more bespoke or disease-specific donor cohorts.

Overall, there is a flexible range of options available, allowing users to balance experimental customisation with robustness and confidence, depending on their experience level and study.

---

Q9

**What is the range of flow rate (ml/min) in the PhysioMimix Core System?**

PhysioMimix Core supports fully adjustable, recirculating intra- and inter-organ flow rates that can be tuned to match physiological conditions for different tissues and study designs, rather than being limited to a single fixed flow range.

In the PhysioMimix Core System, flow rate is controlled and specified in microlitres per second (µL/s). The current operating range is 0.5 to 2.5 µL/s. Converted into millilitres per minute, this corresponds to a flow range of approximately 0.03 to 0.15 mL/min (that is, 30 to 150 µL/min).

---

Q10

**Can the PhysioMimix DILI assay be used to demonstrate no potential for DILI?**

Yes, absolutely. At the core of toxicology is the principle that “the dose makes the poison”, and as a result, Drug-induced liver injury (DILI) exists across a spectrum rather than as a binary outcome.

One of the key strengths of the PhysioMimix Core’s DILI assay is its ability to detect and characterise that full range of responses. As shown earlier, we have tested a wide range of compounds in the System, spanning high DILI risk through to low DILI risk, and importantly, everything in between. This means the assay can capture situations where compounds show minimal or no evidence of liver injury under relevant exposure conditions.

The system allows us to observe sensitive, multiparametric readouts, rather than relying solely on cell death as an endpoint. Instead of asking whether cells simply survive or not, we can measure changes in liver functionality, stress markers, and other sub-toxic responses that occur well before overt injury.

That capability, to detect subtle, graded changes in function across a range of doses, makes the PhysioMimix Core's DILI assay a particularly powerful tool. It supports a more nuanced and scientifically robust assessment of DILI risk, including providing confidence when a compound shows a low or negligible risk profile within the tested exposure window.

---

Q11

**Can you look at the steatosis or fibrosis in your model?**

Yes, absolutely. We have a well-established (**Metabolic dysfunction-associated steatohepatitis(MASH) model** on the PhysioMimix platform that enables the study of both steatosis and fibrotic progression. Steatosis is induced using a proprietary hepatosteatosis-inducing medium, which we have developed and validated internally to drive lipid accumulation in hepatocytes derived from healthy donors.

To model fibrosis, the system incorporates a multi-cellular co-culture, bringing together hepatocytes, Kupffer cells, and hepatic stellate cells. This combination recreates the relevant microenvironment and cellular cross-talk required to drive both steatotic and fibrotic phenotypes *in vitro*. The resulting model enables the investigation of disease-relevant mechanisms, as well as compound effects, in a physiologically meaningful context.

This MASH model has been widely adopted across multiple organisations and use cases. Importantly, it has also previously supported data submissions as part of an Investigational New Drug (IND) package, **Inipharm's INI-822 for metabolic liver disease treatment**, demonstrating its relevance and maturity for translational and regulatory-adjacent applications.

---

Q12

**Can you test and compare dose concentration schedules using the PhysioMimix Core?**

Yes, absolutely. The PhysioMimix Core platform is highly flexible and well suited to this type of investigation. It's Multi-chip plates use an open-well format, which allows us to dose and sample repeatedly over the course of an experiment. This means dosing schedules can be readily adjusted to reflect the specific requirements of a given compound, including different concentrations, frequencies, and exposure durations.

The system also offers strong experimental capacity through its range of plate formats. We routinely use **Liver-12 and Liver-48**

**Multi-chip plates**, which provide sufficient replicates to explore multiple dose concentrations and conditions within a single study. For DILI assessments specifically, we typically test around six concentrations as standard, enabling a robust view of dose–response behaviour.

Where MPS delivers the greatest value is later in the pipeline, when you have shortlisted a small number of lead candidates and have a clearer sense of the exposure range that is clinically or biologically relevant. Testing those defined concentrations and dosing regimens in an MPS provides a highly effective and informative use of the technology. If the goal is to explore a broader dose range or more complex schedules in parallel, then higher-throughput configurations such as Liver-48 (offering up to 288 samples per run capacity) are particularly powerful. They allow expanded concentration or regimen comparisons while still maintaining the mechanistic depth and physiological relevance of the model.

**Please view our Application Note "Accelerating DILI prediction: A high-throughput Liver-on-a-chip solution" for more information**

---

Q13

**How does the MPS system handle drugs that are sticky and adhere to glassware?**

The PhysioMimix platform is designed to minimise issues associated with compound adsorption.

All PhysioMimix Multi-chip consumable plates are manufactured from cyclic olefin copolymer (COC), a material with low non-specific binding properties. COC was specifically selected to avoid adsorption effects, which reduces the risk of compound adsorption, a challenge often seen for hydrophobic or "sticky" drugs, to ensure more consistent and reliable results.

It is important to note, unlike many other MPS platforms, PhysioMimix Core's consumables do not use Polydimethylsiloxane (PDMS), which is known to absorb small molecules.

As a result, PhysioMimix performs well with compounds that typically adhere to glassware or elastomer-based systems, supporting more accurate dosing and improved data interpretation.

Please view our **Technology page** for more information about our Multi-chip plate-based design

---

Q14

**Does your team have experience introducing PBMCs into Liver MPS?**

Yes, this is an area we are actively working on. We have already completed proof-of-concept studies demonstrating that peripheral blood mononuclear cells (PBMCs) can be successfully introduced and circulated within the PhysioMimix System.

Specifically, we have shown that PBMCs can be maintained under recirculating flow conditions in both our Barrier and Liver plates, and importantly, that they can be recovered at the end of an experiment for downstream profiling. This is a critical aspect when studying immune-related mechanisms and responses.

We are currently continuing to optimize this workflow. As part of that effort, we have run proof-of-concept experiments using two antibodies to investigate immune-mediated DILI, and the early results are very encouraging. We are planning to share more of this data at conferences over the course of the year.

While the assay is still in development, our aim is to further mature and validate it, with the intention of moving toward commercial availability later in the year. I won't go into more detail at this stage, but it is definitely an area to watch, and one that we are invested in heavily.

# Resources hub

Dive deeper into our technology, its applications, and how its helping enhance the development of tomorrow's medicines around the world


Webinars


App notes


Posters


Scientific Papers


Brochures


SOPs

**cn-bio.com/resources**

CN-BIO

**+44 (0) 1223 737941** | **sales@cn-bio.com**

visit **cn-bio.com**