CN-BIO

2026 WEBINAR SERIES > S9E3

Improving Oral Bioavailability Prediction with Human Models

Q&A

A full run down of questions & answers from our October 1st webinar

Abbreviations

Absorption, distribution, metabolism and excretion **(ADME)**

Alanine aminotransferase **(ALT)**

Artificial intelligence **(AI)**

Aspartate aminotransferase **(AST)**

Belgian Nuclear Research Center **(SCK CEN)**

Blood–brain barrier **(BBB)**

Central nervous system pharmacokinetics **(CNS-PK)**

Chimeric antigen receptor T cell **(CAR-T)**

Clinical decision support system **(CDSS)**

C-X-C motif chemokine ligand 10 **(CXCL10)**

Cytochrome P450 **(CYP)**

Drug–drug interaction **(DDI)**

Drug-induced liver injury **(DILI)**

Drug metabolism and pharmacokinetics **(DMPK)**

Fraction absorbed **(Fa)**

Fraction escaping gut metabolism **(Fg)**

Fraction escaping hepatic metabolism **(Fh)**

Inflammatory bowel disease **(IBD)**

Interferon gamma-induced protein 10 **(IP-10)**

In vitro to *in vivo* extrapolation **(IVIVE)**

Irritable bowel syndrome **(IBS)**

Lactate dehydrogenase **(LDH)**

Metabolic dysfunction-associated steatohepatitis **(MASH)**

Microphysiological system **(MPS)**

New approach methodologies **(NAMs)**

Oral bioavailability **(F)**

Organ-on-a-chip **(OOC)**

Pharmacokinetic **(PK)**

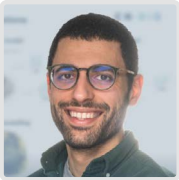
Physiologically based pharmacokinetic **(PBPK)**

Proteolysis Targeting Chimera **(PROTAC)**

Q&A participants



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You can watch this webinar **on-demand here**

Another question?

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

Questions

Q1

Why is mechanistic insight important in DMPK?

Mechanistic insight is important in drug metabolism and pharmacokinetics (DMPK) because it helps explain not only what is happening to a drug but also how and why it is happening. Many customers approach our **Contract Research Services** team because they have observed an unexpected result in an *in vitro* study, an animal model, or in the clinic and need to understand the underlying biology. Knowing the overall disposition of a drug is valuable, but identifying the contribution of specific processes—such as intestinal absorption, transporter activity, gut metabolism, hepatic uptake, metabolism, and clearance—can help resolve unexpected findings and determine the most appropriate next step. At CN Bio, we use our PhysioMimix® primary human **Gut/Liver microphysiological system** (MPS), also known as a Gut/Liver-on-a-chip, to study these processes in a connected, dynamic environment that more closely reflects first-pass drug disposition. The resulting data can be combined with computational modeling to derive gut- and liver-specific absorption, distribution, metabolism and excretion (ADME) parameters and provide more informative inputs for physiologically based pharmacokinetic (PBPK) models. This can improve the translation of non-clinical findings to human exposure, support investigations into **oral bioavailability** and drug–drug interactions (DDIs), and help guide decisions regarding compound optimization, formulation, dose selection, and clinical development.

Read **our visual guide to improving oral bioavailability prediction** for more info.

Q2

Why is understanding DDI important in both the gut and the liver?

DDI assessment is important because it is key to understanding whether there is any risk when two drugs are prescribed at the same time. Understanding DDIs in both the gut and the liver is important because it helps determine not only whether an interaction is occurring but also where it occurs. This is particularly relevant for orally administered drugs, which pass through the gut before reaching the liver. Although DDIs are often studied in

the liver because it is a major site of metabolism and clearance, interactions can also arise in the gut through enzymes expressed in enterocytes or transporters that are highly expressed in intestinal cells (as in the dabigatran etexilate example). Studying the gut and liver together allows us to distinguish gut-specific from liver-specific effects and understand the contribution of each site. For example, if a compound affects a gut transporter, **a coupled Gut/Liver system** can show how that interaction alters the compound's availability as it passes through the gut and is subsequently metabolized in the liver. This provides a more complete understanding of the DDI and its overall impact on **oral bioavailability**.

Read **our visual guide to improving oral bioavailability prediction** for more info.

Q3

How do you calculate ADME parameters?

We begin with the experimental concentration–time course data generated in the study. Our *in silico* modeling component is then used to reproduce and fit that experimental data. From the fitted model, we can derive ADME parameters, including gut and liver clearance, apparent permeability based on gut absorption, and metabolite formation. These parameters can then be appropriately scaled to calculate the fraction absorbed (Fa), the fraction escaping gut metabolism (Fg), and the fraction escaping hepatic metabolism (Fh). Together, these values can be used to estimate the drug's overall oral bioavailability (F).

Read the publication by Abbas et al., 2025, detailing the process using midazolam as a tool compound here.

Q4

Which *in silico* tools do you use to translate MPS data into clinical dose predictions?

This follows a similar process to the one described above. We combine the data generated by the MPS with computational modeling. Although these models can take different forms, our traditional workflow involves using MPS data to build a mechanistic model describing how a particular compound moves through the system. From this model, we can derive a range of ADME parameters. More recently, we have been working on incorporating these parameters into physiologically based models, such as PBPK models. In summary, we start with the MPS data, translate it into a mechanistic model, and then use the resulting parameters as inputs for a PBPK model to support clinical dose prediction.

Read the publication by Abbas *et al.* detailing the process using midazolam as a tool compound here.

Read our blog: Integrating in silico tools with Organ-on-a-chip to advance ADME studies

Q5

How does MPS-derived data inform dosing strategies?

Powered by our **PhysioMimix Core platform**, the connected Gut/Liver MPS can generate human-relevant data on absorption, first-pass metabolism, clearance, and bioavailability. When integrated with PBPK modeling, these data can help compare dose levels, formulations, and dosing frequencies, support starting-dose selection, and identify situations (such as drug interactions or impaired liver function) where exposure may change. The model does not prescribe a clinical dose on its own, but it can provide a stronger mechanistic basis for dosing decisions and reduce uncertainty before entering the clinic.

Q6

Is your bioavailability model currently being used by pharmaceutical or biotechnology companies?

Yes, we have an active base of European and US pharmaceutical and biotechnology companies using the Gut/Liver MPS and **bioavailability assay** via different routes. Some work with our Contract Research Services team, particularly when they have more challenging compounds, formulation-related questions, or want to use a mechanistic model to understand their compounds' bioavailability. We have helped to solve many problems for clients in this way. Others have a PhysioMimix Core System in their own laboratories, which they use in their drug discovery programs. Therefore, the model is used both in-house by customers and through our Contract Research Services.

Click the links for more information on our **ADME Contract Research Services**, or to **contact us**.

Q7

At what stage in the development process would you approach CN Bio with a project?

Ideally, the model is used in-house during lead optimization to inform compound selection and development decisions as the program progresses. Clients usually approach our Contract Research Services team when they have narrowed their

pipeline to a small number of candidate molecules and want to mechanistically assess oral bioavailability to inform which to take forward before entering first-in-human clinical trials. We also work with clients whose earlier data are difficult to interpret, or whose animal studies have produced conflicting results (for example, bioavailability of 30% in dogs compared with 70% in rats). In these cases, the model can provide the mechanistic data needed to better understand human oral bioavailability and inform dosing strategy before entering the clinic.

Click the links for more information on our **ADME Contract Research Services**, or to **contact us**.

Q8

Approximately how many compounds have you evaluated in terms of the correlation between MPS-based predictions and human data?

The number of compounds that we have tested via internal R&D using the Gut/Liver model is around 10–15, but obviously we have evaluated many more through our **Contract Research Services**. Unfortunately, these are confidential, so we can't share them more widely. Our pharma customers have conducted their own evaluations using their tool compounds, and we expect supplementary datasets from strategic partners soon.

Q9

You mentioned the Roche drug metabolism study of 15 compounds, but you did not discuss the results. Can you briefly comment on that?

The Roche study evaluated the PhysioMimix Liver MPS, also known as **Liver-on-a-chip**, for quantitative **drug metabolism** using 15 compounds spanning CYP-, UGT-, and aldehyde oxidase-mediated pathways. Extended culture enabled clearance measurements of low-turnover compounds and the detection of complex metabolite profiles that are difficult to investigate in conventional short-duration assays. Of the 12 compounds taken forward into *in vitro-to-in vivo* extrapolation (IVIVE), seven were predicted within 3-fold of observed human hepatic intrinsic clearance. The study also showed that combining experimental data with mechanistic modeling could estimate the contribution of individual metabolic pathways and improve interpretation of perfused-system data. Overall, the work demonstrated the platform's potential to measure challenging compounds, provide mechanistic insight, and support translation toward humans. However, it should be noted that this was an exploratory study using a single hepatocyte donor.

Further details are available in **Docci *et al.*, "Exploration and Application of a Liver-on-a-Chip Device in Combination with Modelling and Simulation for Quantitative Drug Metabolism Studies," *Lab on a Chip*, 2022, 22(6):1187–1205.**

Q10

Can the PhysioMimix platform be used for oral absorption modeling?

Oral absorption modeling combines experimental data with computational models to predict how much and how quickly a compound is absorbed after oral dosing. PhysioMimix can use a Gut-only MPS assay to investigate intestinal permeability, transport, and gut-wall metabolism, or a **connected Gut/Liver MPS** to additionally assess first-pass hepatic metabolism and clearance. The latter helps to identify why a compound has limited bioavailability and provides human-relevant parameters for **PBPK modeling**.

Q11

Could the PhysioMimix platform also be extended to kidney models to investigate renal clearance, excretion, and nephrotoxicity?

Yes. Kidney models are an important extension because they can provide information on renal transport, metabolism, excretion, and nephrotoxicity, offering a more complete view of how a compound is absorbed, metabolized, and eliminated in humans.

CN Bio is also exploring kidney-model development through an Innovate UK-funded project delivered in partnership with the NC3Rs. The project is assessing the feasibility of incorporating a human kidney model into the PhysioMimix platform to generate mechanistic renal-clearance and excretion parameters that can be integrated with Gut/Liver data and translated into PBPK models. This remains a feasibility and development program, rather than an established commercial CN Bio assay, and is part of a wider project to reduce animal use in pharmacokinetic (PK) studies in line with the **UK government's plan** to reduce the use of dogs and non-human primates in dedicated PK studies by at least 35% by 2030. **Read the press release here**.

Researchers at Texas A&M have utilized the PhysioMimix® platform to develop a renal proximal tubule model for kidney transport and nephrotoxicity studies, demonstrating the platform's potential to support new organ models and applications.

View their poster here.

Q12

Have you also identified any characteristics of compounds that tend to be well predicted by the MPS as well as those that tend to be more difficult to predict accurately?

We have tested a series of different drug modalities in our Gut/Liver MPS with confidence. As we showed in the webinar, we have mechanistically handled some quite difficult drug stories, and you can still unpick the data quite nicely. In particular, insoluble drugs are quite difficult for *in vitro* methods in general, but we wouldn't specifically call out any modalities that have performed less well in the system once optimized.

Q13

Do you have any examples of applying the dual-organ system to deconvolute parameters that limit the oral bioavailability of PROTACs and to optimize ADME parameters?

We have explored the application of our Gut/Liver MPS with Proteolysis Targeting Chimeras (PROTACs) in an unpublished pilot study. In this study, we observed measurable transport across the gut barrier, along with significant retention of the compound within the intestinal cell layer, as determined by cell lysate analysis. However, the amount of PROTAC in the gut basolateral compartment was insufficient to fully assess its bioavailability; therefore, further optimization is needed to improve its absorption.

Following optimization, we think the assay could help distinguish whether limited oral exposure with PROTACs is driven primarily by absorption, intracellular accumulation, metabolism, or downstream hepatic clearance.

Q14

I would like to know how all of this applies to herbal medicine, not just pharmaceutical drugs, from absorption through metabolism.

The same principles of absorption, metabolism, exposure, and toxicity apply to herbal medicines as to pharmaceutical drugs. Human Gut/Liver MPS could assess which constituents cross the intestinal barrier, how they are metabolized, their potential **liver toxicity**, and whether they interact with enzymes or transporters.

Because herbal preparations are complex mixtures that can vary by source, processing, and dose, studies require chemically characterized, standardized preparations and suitable analytical controls.

Q15

Could MPS be applied to investigate the DMPK of radiopharmaceuticals?

Radiopharmaceutical DMPK depends on the stability and behavior of the complete construct: the targeting molecule, linker, and radionuclide. Metabolism or radionuclide release can alter biodistribution, clearance, and radiation exposure to healthy organs, so conventional PK measurements should be combined with imaging and dosimetry. Liver and kidney MPS could potentially provide mechanistic data on metabolism, organ uptake, clearance, and toxicity, but CN Bio has not yet validated its models for radioactive compounds, so this remains a potential future application rather than a current assay.

Q16

What is your experience with exposure prediction for other routes of administration? Does the GastroPlus PBPK model help? Do you have any insights to share?

Our work to date has focused primarily on predicting exposure for orally administered compounds using the Gut/Liver model. The PBPK studies we have conducted have used open-access models, but the resulting parameters can also be used as inputs for other platforms, such as Simulations Plus' GastroPlus or Certara's Simcyp. The parameters we generate are therefore not specific to a particular PBPK provider. We are also exploring the **integration of a kidney model** with the Gut/Liver system to study absorption, metabolism, and renal excretion within a single workflow. This will provide a broader set of human-relevant parameters to inform more advanced physiologically based models.

Q17

Can *in vitro* systems address issues with poorly soluble drugs that, in vivo, are exposed to different environments, such as acidic to neutral, over different exposure times? How can these issues be explored *in vitro*?

Working with a poorly soluble compound is always challenging, and an *in vitro* system can help determine whether poor solubility is limiting absorption. If it is, formulation-based strategies, such as encapsulation, can be explored to improve solubility. A Gut/Liver MPS-based approach can then be used to compare specific formulations and assess their impact on bioavailability. For example, clients have approached us with two different formulations and asked us to investigate how each affects the bioavailability of their

compound. We do not, however, have evidence to support using this approach to reproduce the changing pH environments and transit times a compound experiences *in vivo*.

Q18

Would this dual Gut/Liver MPS be able to discriminate between different enabling formulations aimed at improving oral bioavailability?

Through our in-house **ADME Contract Research Services**, we have experience discriminating between different customer formulations. One example involved comparing a drug with and without a lipid-based excipient to demonstrate how the model can be used for this purpose. We have not yet used the model to assess the bioavailability of amorphous solid dispersions. However, as it is essentially a cell-based system, compounds can be dosed in different formats. Therefore, if a formulation is compatible with a **traditional Caco-2 model**, where different formulations are added to the medium, it should also be compatible with this system.

Q19

Comment on the utility of micelles in drug delivery

Micelles can improve the apparent solubility and delivery of poorly water-soluble compounds, potentially increasing the amount available for intestinal absorption. However, we do not currently have specific data demonstrating the use of micellar formulations in our Gut/Liver MPS.

In principle, the system could be used to compare a micellar formulation with an unformulated compound or an alternative formulation and assess its effect on absorption and downstream bioavailability. Feasibility would first need to be established, including compatibility of the micelle components, dosing vehicle, and concentration with the cell-based assay.

Please contact us if you would like to investigate this further.

Q20

Can MPS support the development of advanced drug-delivery systems, such as nanoparticles and liposomes, and their evaluation in oncology, including tissue penetration, targeted delivery, biomarkers, metastasis and cell therapies such as CAR-T and CAR-NK?

The adaptability of the PhysioMimix platform may enable researchers to develop fit-for-purpose models for aspects of

advanced drug delivery and oncology, depending on the route of administration, target tissue, and experimental question. Potential applications could include vascular transport, tissue penetration, cellular uptake, local exposure and toxicity, alongside endpoints such as tissue viability, barrier integrity, inflammatory signaling, histopathology, immunohistochemistry and biomarker analysis.

Through a collaboration with **Melomanes**, a European Union-wide consortium developing an immunotherapy that pairs anti-human leukocyte antigen-G chimeric antigen receptor T (CAR-T) cells with magnetic nanoparticles capable of inducing localized hyperthermia, CN Bio has also completed exploratory, non-validated work using a perfused melanoma-on-a-chip model to develop CAR-T cell therapy for solid tumors. This illustrates the platform's potential for studying immune-cell trafficking, endothelial barrier crossing, tumor infiltration, and cytotoxic activity under flow. **Read the blog here.**

Customers at the University of Pittsburgh also adapted the PhysioMimix platform for oncology research. A study of the metastatic liver microenvironment by Clark et al. showed that IP-10/CXCL10 could trigger the emergence of dormant breast cancer cells, demonstrating how customer-developed models can be used to investigate metastasis and associated biomarkers. **Read the publication here.**

Customers at the Belgian Nuclear Research Center (SCK CEN) have also adapted the platform to culture patient-derived rectal tumor organoids and investigate responses to fractionated radiotherapy, including changes in barrier integrity and treatment-response biomarkers. This provides another example of how PhysioMimix can support customer-developed oncology models beyond CN Bio's validated applications. **Read the publication here.**

Watch our animation to discover PhysioMimix Core's adaptability here.

Q21

In the CYP2D6 study, are the levels of the protein the same between the 3 donors?

We did not measure CYP2D6 protein levels in the three donors, so we cannot confirm whether they were the same. We are interested in assessing CYP2D6 expression at the RNA level, as this is a more accessible and cost-effective approach. However, RNA expression does not always directly correlate with protein abundance or enzyme activity. In this study, drug clearance provides a functional

readout of CYP2D6 activity and is therefore more relevant to understanding donor-specific differences than measuring protein levels alone.

Q22

Can PhysioMimix MPS also be used to assess liver toxicity?

Yes. The connected Gut/Liver MPS can, in theory, indicate hepatic toxicity alongside ADME/DMPK measurements, helping to show whether intestinal absorption and first-pass metabolism lead to liver exposure or the formation of toxic metabolites. However, most of CN Bio's extensive work on drug-induced liver injury (DILI) has used validated **Liver-only models** comprising primary human hepatocytes and Kupffer cells under perfusion. These models support longer-term repeat-dose studies and measure clinically relevant endpoints such as ALT/AST, LDH, albumin, and urea to assess DILI.

CN Bio has also undertaken exploratory work incorporating circulating immune cells into Liver-on-a-chip models to investigate **immune-mediated liver injury**. This is not as extensively validated as the core hepatocyte–Kupffer cell DILI assay, but it demonstrates how the platform can be adapted to study more complex immune-related mechanisms.

The Liver MPS is also contributing to a 3Rs Collaborative-led, FDA-CDER cross-platform project evaluating commercially available liver MPS for DILI. Known hepatotoxicants and matched controls are being tested using a common protocol to assess category-level performance, variability, and reproducibility. The project's Letter of Intent was accepted into the FDA's ISTAND program in January 2026, allowing it to progress through the qualification process for a defined context of use. **Watch the webinar "Building confidence for regulatory decision-making with immune competent models" for more info here.**

Read the first publication "Introduction to the 3RsC's cross-platform MPS evaluation for DILI in collaboration with FDA-CDER" here.

Read our ebook: A technology guide to assessing liver safety with microphysiological systems

Q23

What are the most comprehensive tests to identify efficacy and risk vs benefit of a substance for an individual?

A comprehensive MPS-based assessment would combine information on DMPK, efficacy, and safety. This could include intestinal absorption and bioavailability, hepatic metabolism and clearance, metabolite formation, pharmacological activity in the target tissue, and potential toxicity in relevant organs. Computational approaches, such as PBPK modeling, can then integrate these data to predict human exposure and inform dose selection.

Human MPS can bring several of these measurements into a connected experimental workflow. The Gut/Liver system, for example, investigates absorption, first-pass metabolism, and hepatic exposure. However, separate disease- or organ-specific MPS models are currently used to individually assess efficacy and toxicity at clinically relevant concentrations. In the future, a powerful use of MPS technology would be to connect additional models, such as kidney, target-tissue, or disease models, to form highly advanced human-relevant systems. These would provide a broader picture of drug disposition and organ-specific risk in one PKPD-based test.

However, even if MPS technology could be developed in this way, no single assay could fully determine the risk–benefit profile of a substance for an individual. Individual response is also influenced by genetics, age, sex, disease state, organ function, concomitant medication, and other factors. MPS incorporating cells from different donors or patient-relevant disease phenotypes can help investigate aspects of this variability, but they should be viewed as part of an integrated evidence package rather than a complete personalized prediction.

Q24

Can this model also mimic lymphatic transport and how it allows compounds to escape the hepatic first-pass effect?

Compounds absorbed through the intestinal lymphatics can partially bypass the portal circulation, thereby reducing hepatic first-pass exposure before entering the systemic circulation.

Our Gut/Liver MPS model can assess intestinal absorption, gut-wall metabolism, and subsequent hepatic metabolism via the portal route, but it cannot currently distinguish or quantify the proportion of a compound entering the lymphatic circulation because it lacks a lymphatic compartment.

Q25

What do you think about sublingual drug dosing compared to oral administration given the gut barriers? Do you have a model for sublingual dosing?

Sublingual dosing can offer advantages over conventional oral administration because the drug is absorbed through the oral mucosa directly into the systemic circulation. This can provide a faster onset of action and may avoid gastrointestinal degradation, intestinal barriers, and some hepatic first-pass metabolism. However, its suitability depends on the compound, as the available absorption area is limited and factors such as dose size, solubility, permeability, and residence time in the mouth can restrict delivery.

Our current Gut/Liver MPS is designed to investigate orally administered compounds that undergo intestinal absorption and first-pass metabolism. We do not currently have a model of the sublingual mucosa, so we cannot directly assess sublingual absorption or experimentally compare the two routes. However, data generated using an appropriate oral-mucosal model could potentially be combined with downstream human liver MPS data and/or computational models to support exposure predictions for sublingual dosing.

Q26

How does a compromised liver (fibrotic or cirrhotic) affect drug metabolism?

A compromised liver can alter drug metabolism in several ways. Fibrosis and cirrhosis can reduce the number and function of hepatocytes, change the activity of drug-metabolizing enzymes and transporters, and disrupt hepatic blood flow. Together, these effects can reduce clearance, increase systemic drug exposure, and prolong a drug's half-life, although the extent of the change depends on the compound, the metabolic pathway involved, and the severity of the liver disease.

Investigating this *in vitro* is an area where human-relevant disease models could add value, although it is not an avenue we have tested. CN Bio's **Liver-on-a-chip MASH model**, for example, combines primary human hepatocytes, Kupffer cells, and hepatic stellate cells to recapitulate key features of progressive liver disease, including steatosis, inflammation, and a measurable fibrosis phenotype. It could therefore be used to investigate how a diseased liver responds differently from a healthy liver, including changes in drug metabolism and susceptibility to drug-induced liver injury. However, while the model captures fibrosis associated with MASH, we would not describe it as a model of advanced cirrhosis.

Q27

What metabolic differences between males and females should be considered in therapeutic development?

Biological sex can influence drug ADME through differences in gastrointestinal transit, body composition, renal function, hormones, and hepatic enzyme and transporter activity. These differences may affect drug exposure, clearance, efficacy and adverse-effect risk.

However, sex is only one source of variability; genetics, age, disease, hormonal status, concomitant medicines, and environmental factors may be equally important. These findings should not be treated as universal male–female rules.

Human MPS allows gut and liver models using cells from male and female donors to be compared under controlled conditions, including differences in absorption, transport, metabolism and toxicity. Multiple donors are needed to distinguish sex-related effects from normal interindividual variability.

This approach could help identify whether sex should be included as a development variable and provide mechanistic data to support clinical-trial design, PBPK modeling and, potentially, dosing strategies.

Q28

What absorption rate considerations need to be made for IBS patients?

Irritable bowel syndrome (IBS) may affect the rate and consistency of oral drug absorption by altering gastrointestinal motility and transit time. Faster transit in diarrhea-predominant IBS may reduce the time available for dissolution and absorption, while slower transit in constipation-predominant IBS may delay peak exposure. The effect varies by patient, compound, and formulation.

Human intestinal MPS could help assess permeability and transport under controlled, disease-relevant conditions but would not recapitulate whole-gut motility. This gut–liver–immune study by Trapecar *et al.* demonstrates how MPS can investigate intestinal barrier and microbiome-related effects, although it modeled inflammatory bowel disease (IBD) rather than IBS.

Read the publication: Gut-Liver Physiomimetics Reveal Paradoxical Modulation of IBD-Related Inflammation by Short-Chain Fatty Acids here.

Q29

Do different races absorb drugs differently? If so, which classes of drugs?

Race itself is not a reliable biological predictor of drug absorption. Passive absorption is generally similar, but genetic variants affecting enzymes and transporters can occur at different frequencies across populations and may alter metabolism, efficacy or toxicity. Important examples include clopidogrel, warfarin, codeine, some antidepressants, tacrolimus and certain cancer therapies. The more accurate approach is to study individual genotype and metabolic phenotype. Human MPS using genetically characterized donors could help investigate these differences under controlled conditions.

Q30

Can AI models accurately predict human oral drug exposure when absorption and metabolism parameters vary significantly between species?

Artificial intelligence (AI) can help predict human oral exposure, but only within the limits of the data it is trained on. If absorption and metabolism differ substantially between species, animal data alone may produce unreliable human predictions. Combining AI with mechanistic PBPK modeling and human Gut/Liver MPS data provides a stronger approach because the model is anchored in human-relevant absorption and metabolism rather than relying solely on cross-species extrapolation.

Q31

Are any animal models useful, or do you prefer models based on human tissues?

New approach methodologies (NAMs) are becoming increasingly important, but it is unlikely that NAMs, which include **Organ-on-a-chip (OOC) technologies**, will completely replace animal models in the near term, as animal studies remain deeply embedded in drug discovery. However, technologies such as MPS and OOC (an alternative name for MPS) can help reduce both the number of animals required and the wider reliance on animal studies during non-clinical drug discovery and development. They can also provide human-relevant information to support a better-informed strategy before progressing into animal studies and, ultimately, the clinic. Historical data suggest that non-human primates are the closest animal predictors of human oral bioavailability, while other commonly used species, including dogs and rats, show

poorer correlation. For example, a 2014 study by Musther *et al*., "Animal versus human oral drug bioavailability: do they correlate?" reported an overall animal-to-human correlation of $R^2 = 0.34$. A like-for-like replacement of animal models is unlikely in the near term, but combining human-relevant approaches with animal data could support a more informed strategy before clinical dosing to minimize risk. **Read the publication here.**

For predicting human outcomes, we prefer to use primary human microtissues as the anchor. However, animal-derived cells can be used to create species-specific MPS for rats, dogs, or other species. This allows compounds to be tested under comparable experimental conditions across species. We have not developed animal-MPS models for ADME/DMPK use; however, we have demonstrated their use for evaluating drug-induced liver injury (DILI). We have run comparable assays using primary human, rat, and dog hepatocytes, measuring endpoints such as ALT, LDH, albumin, and urea. Comparing the same compound in human and animal MPS can reveal whether a toxicity response is conserved across species or specific to one species. This can help to guide selection of the most relevant species for subsequent studies, explain conflicting animal findings, and strengthen *in vitro–in vivo* extrapolation.

For more information, read our Application Note: Enhance IVIVE with cross-species Liver MPS DILI assays here.

Q32

Please comment on the relevance and importance of 'species differences' (dogs, guinea pigs, rabbits, rats, mice).

Species differences are highly relevant because dogs, guinea pigs, rabbits, rats, and mice can differ substantially from humans (and from one another) in terms of physiology. The same compound may show markedly different oral bioavailability across species, and no single animal species is consistently predictive of human pharmacokinetics. This is best exemplified by Musther *et al*. (2014), whose interspecies variability study reported an overall animal-to-human correlation of $R^2 = 0.34$. **Read the publication here**.

Animal studies can provide useful information, particularly when the species is selected for a specific biological or mechanistic question. However, results need to be interpreted in the context of the relevant species differences rather than extrapolated directly to humans. Human-relevant MPS complements animal data by determining whether results are species-specific, and by providing mechanistic insight into the intestinal and hepatic processes most

likely to influence human oral bioavailability. This supports more informed translation and reduces uncertainty before clinical dosing.

Q33

Can CN Bio's models test for blood–brain barrier access of drugs?

CN Bio does not currently offer a validated blood–brain barrier (BBB) model, so our established assays cannot directly determine whether a compound enters the brain. However, our customers are using the **PhysioMimix® platform** to develop their own BBB models.

The PhysioMimix platform is **designed to be adaptable**, enabling researchers to incorporate various human cell types and configure novel tissue models under perfusion conditions. This flexibility can support the development of customer-specific BBB models to assess endpoints such as barrier integrity, permeability, and transporter-mediated drug movement.

CN Bio's validated Gut/Liver MPS can complement these models by characterizing oral bioavailability and the metabolites available to reach the brain. Combining this data with a customer-developed BBB model and PBPK or central nervous system pharmacokinetics (CNS-PK) modeling could provide a more complete picture of systemic exposure and brain penetration.

Q34

Is there an opportunity to develop CDSS in neurology for therapy response?

There may be an opportunity for MPS data to support research into future neurology-focused clinical decision support systems (CDSSs), but PhysioMimix is a research-use platform and is not registered for clinical use. Any data generated would therefore contribute to non-clinical research, model development, or validation rather than directly informing treatment decisions for individual patients.

Q35

Why don't we study where most of our genetic material comes from (i.e., bacteria, fungi, archaea, and viruses) rather than metabolism and health?

CN Bio's current Gut/Liver MPS does not contain a complete living microbiome, so it cannot reproduce the full genetic and metabolic contribution of bacteria, fungi, archaea, and viruses. However, microbiome-derived metabolites can be introduced

experimentally. In the Trapecar study mentioned in question 28, a gut–liver–immune MPS was used to investigate how microbiome-derived short-chain fatty acids affected intestinal barrier function, inflammation, and downstream liver biology. This illustrates how MPS can potentially help to separate and study specific microbiome–host interactions under controlled, human-relevant conditions.

Read the publication: Gut-Liver Physiomimetics Reveal Paradoxical Modulation of IBD-Related Inflammation by Short-Chain Fatty Acids here.

Q36

Drugs in breast milk

Measuring transport across the blood–milk barrier is not currently a CN Bio capability.

To recreate the PhysioMimix Gut/Liver model in your lab, you need:



PhysioMimix Core



Multi-chip Dual-organ plates

Find out more about our ADME Contract Research Services

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