Emerging Role of Organ-on-a-Chip Technologies in Quantitative Clinical Pharmacology Evaluation

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The recently enacted Prescription Drug User Fee Act (PDUFA) VI includes in its performance goals “enhancing regulatory science and expediting drug development.” The key elements in “enhancing regulatory decision tools to support drug development and review” include “advancing model-informed drug development (MIDD).” This paper describes (i) the US Food and Drug Administration (FDA) Office of Clinical Pharmacology’s continuing efforts in developing quantitative clinical pharmacology models (disease, drug, and clinical trial models) to advance MIDD, (ii) how emerging novel tools, such as organ-on-a-chip technologies or microphysiological systems, can provide new insights into physiology and disease mechanisms, biomarker identification and evaluation, and elucidation of mechanisms of adverse drug reactions, and (iii) how the single organ or linked organ microphysiological systems can provide critical system parameters for improved physiologically-based pharmacokinetic and pharmacodynamic evaluations. Continuous public-private partnerships are critical to advance this field and in the application of these new technologies in drug development and regulatory review.

The US Food and Drug Administration Reauthorization Act (FDARA)† of 2017 includes the reauthorization of the Prescription Drug User Fee Act (PDUFA) that provides the US Food and Drug Administration (FDA) with the necessary resources to maintain a predictable and efficient review process for human drug and biologic products. The provisions in PDUFA VI continue to include “enhancing regulatory science and expediting drug development” to build on the success of the FDA’s regulatory science program. The US FDA Office of Clinical Pharmacology (OCP) has accordingly set the Office goals to enhance drug development, promote regulatory science and innovation, and inform the safe and optimal use of medications. To achieve these goals, the Office strives to play a pivotal role in advancing development of innovative new medicines by applying state-of-the-art regulatory science and clinical pharmacology principles, and to promote therapeutic optimization and individualization through best practices in research, policy development, and drug evaluation throughout the product cycle.3 In OCP’s Good Review Practices,4 there are four key questions to address in the clinical pharmacology review: (i) To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness? (ii) Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought? (iii) Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors? (iv) Are there clinically relevant food–drug or drug–drug interactions (DDIs), and what is the appropriate management strategy? To address these key clinical pharmacology questions, modeling and simulations play a critical role in the review and analyses,5 and experimental data are needed from various preclinical and clinical studies to aid in this exercise. Figure 1 depicts quantitative clinical pharmacology models that are currently being used in drug development and regulatory review.6,7

Disease models are developed to quantify disease progression with placebo or drug treatment and need to incorporate relevant clinical end points or biomarkers to inform clinical trial design. Drug models, on the other hand, are central to clinical pharmacology review and describe the time course of plasma/tissue concentrations of drugs and/or their metabolites with various dosing regimens, and the relationships between the exposure (or pharmacokinetics (PKs)) and response (or pharmacodynamics (PDs)) for both desired and undesired effects, and individual patient characteristics. The exposure–response relationships are critical to evaluate the benefit–risk ratio of a specific drug treatment or combination of treatments and to provide optimized dosing regimens for patients with various intrinsic (age, gender, race, genetics, hepatic impairment, renal impairment, etc.) and extrinsic (concomitant medications) factors (Figure 1). In addition to disease and drug models, clinical trial models are developed that describe patient adherence and discontinuation and that quantify the patient population covariates important for product safety and efficacy. These trial models are also used to inform the inclusion/exclusion criteria of specific trials that may depend on various factors, such as dosing frequency or convenience related to certain regimens, lack of efficacy, and adverse events.

To enable successful implementation of drug-disease trial models or PK-PD models, we need appropriate biomarkers...
that provide insights into mechanistic underpinnings of disease progression and drug effects. The PK-PD models (Figure 1), depending on the purpose or use, have ranged from simple, linear models, such as those describing drug exposure-QT prolongation relationship, to more complex, mechanistic models, such as physiologically-based...
pharmacokinetic (PBPK) and quantitative systems pharmacology models. Table 1 lists cases of disease and trial models in which various end points and biomarkers have been successfully developed to inform study designs for phase 3 pivotal trials, pediatric trials, combination treatment trials, etc. There is a continued need in end points/biokmarker development to facilitate the development of novel and biosimilar therapeutic proteins and products for rare diseases. The following sections provide insight into the current and future potential use of microphysiological systems (e.g., organ-on-a-chip) in these areas.

**USE OF MICROPHYSIOLOGICAL SYSTEMS (ORGAN-ON-A-CHIP) FOR MECHANISTIC DISEASE, PHARMACOLOGY, AND TOXICOLOGY ASSESSMENT**

As indicated earlier, development and application of mathematical modeling that leverage our understanding of physiology, pathology, and pharmacology to inform drug development has long been appreciated. With the advent of new technologies and innovations in computation, our ability to integrate mathematical models to gain better understanding of disease, drug effects, and inform clinical trial design, and eventually clinical practice, has improved. All these advances bode well for realizing the potential of quantitative systems pharmacology approaches as well as quantitative disease–drug trial models. However, the success of these computational approaches depends on the availability of critical and reliable experimental data that can inform such models. There is a clear need to develop a better understanding of the physiology, disease and its progression, and identification of mechanistic and PD biomarkers that are translatable to outcomes of interest. Better tools are also needed to anticipate and predict drug toxicity. As shown in Figure 2, microphysiological systems can be viewed as an innovative technology that has the potential to enhance the role of quantitative clinical pharmacology in advancing drug discovery and development. To realize the full potential of these emerging technologies, collaboration across various stakeholders in this multidisciplinary setting is essential. Several public-private partnerships in the development and application of various microphysiological systems to evaluate the efficacy, safety, and toxicity of therapies have already been established.

**Physiology and disease**

Microphysiological systems represent advancement over conventional technologies by leveraging the recent advances in microfluidics, microfabrication, and cell biology to better mimic and control the physiological microenvironments. As such, they are more suitable for investigating complex organ-level physiology, tissue architecture, and functions than traditional 2-D cell culture models. This is exemplified by the human breathing lung-on-a-chip, which was used to characterize complex physiological responses, such as activation of endothelial cells, increased expression of adhesion molecules, adhesion, and transmigration of neutrophils across tissue layers and engulfing of bacteria in response to an inflammatory insult by placing bacteria in the alveolar compartment.

Platforms that characterize complex physiology can be leveraged to understand the changes that occur in disease states. Such an application is illustrated by the work done using a neurovascular unit blood–brain barrier (BBB) microfluidic device. This system comprises vascular perfusion channels, barrier membrane, brain compartment, and brain perfusion channels, and was derived using primary human brain-derived microvascular endothelial cells, pericytes, astrocytes, and human induced pluripotent stem cell–(iPSC)–derived human cortical neurons along with co-differentiating astrocytes. Using the system, the authors were able to observe time-dependent changes in the BBB integrity and function, including partial recovery and cytokine activation in response to inflammatory stimulus. By integrating metabolomics and pathway identification analysis, the metabolic signature and pathways associated with the inflammatory stimulation could be mapped. Another example is integration of the human small airway-on-a-chip with a smoke machine and microrespirotrary to study smoke-induced pathophysiology. By lining the device with living human bronchial epithelium from normal and patients with chronic obstructive pulmonary disease, comparative biological responses were obtained that led to the identification of ciliary micropathologies, chronic obstructive pulmonary disease–specific molecular signatures, and epithelial responses to smoke.

Peer-reviewed literature is emerging with examples of disease models using human microphysiological systems (or organs-on-chips). When combined with patient-derived or genetically engineered iPSCs to induce disease-causing mutations, the pathophysiology of rare and ultrarare disease subsets can be elucidated. An example of this is the
work done to elucidate the pathophysiology underlying the cardiomyopathy of Barth syndrome. Using Barth syndrome iPSC-derived cardiomyocytes, the metabolic, structural, and functional abnormalities associated with mutations in the gene encoding tafazzin were defined. The authors further demonstrated with Cas9-mediated genome editing that mutation in the gene encoding tafazzin was sufficient to cause the disease phenotype.\textsuperscript{35} The use of patient-derived cells opens the potential for personalized disease modeling as well as the ability to model the longitudinal progression of the disease both at an individual as well as at the population level.

**Pharmacology**

In the context of drug discovery and development, models that can realistically replicate physiology and disease states are useful in providing reliable inputs for developing systems biology and disease models and have the potential to be transformative. Several current and future applications can be envisioned. Microphysiological systems may provide a reliable means to reproduce the pharmacology and clinically relevant downstream responses of drug treatment. This is particularly useful for lead development and optimization.\textsuperscript{36} Further, microphysiological system platforms that probe higher-order functionality can be very useful for the demonstration of proof-of-concept for new molecular entities early in drug discovery and development. As a proof-of-concept for such an approach, Berdichevsky \textit{et al.}\textsuperscript{37} demonstrated the inhibition of spontaneous electrical excitation of the brain slice treated with a glutamate receptor antagonist, using a microdevice that enables culture of brain slices in separate media formulations while retaining \textit{in vivo} neural network connections and electrophysiological behavior.

\textit{In vitro} models that can reliably demonstrate proof-of-concept are of particular utility in development of drugs for rare diseases for which appropriate animal models are sparse. Such models can be used to characterize the time course of drug effects on the organ-level structure and function and can potentially be used to evaluate the relationship to clinical outcomes of interest. By functionally integrating multiple organs, a more realistic estimate of the clinical response can be projected.\textsuperscript{38} Such an approach combined with patient-derived iPSC has the potential to capture the variability in response stemming from the role of different critical organs that either process the drug of interest (PK) or are the target of the drug effect in the organ of interest (PD).

**Toxicity**

The most common application reported for a microphysiological system is to either predict or characterize the mechanism of on-target and off-target drug toxicity in humans.\textsuperscript{34,39–42} An example of such application is the characterization of hepatotoxicity of several hepatotoxic drugs using human, 3-D, microfluidic, four-cell, sequentially layered, self-assembly liver model.\textsuperscript{32} The system reproduced the acute toxicity (1–2 days) seen with a high concentration of troglitazone as well as the gradual and delayed (28 days) toxicity produced by a lower concentration of troglitazone. In addition, the system could demonstrate the immune-mediated toxicity with trovafloxacin. Such data could inform predictive mathematical models of liver injury. Further, functionally integrating organs provides an opportunity to model the secondary toxic effects of metabolites. This was demonstrated by the functional integration of a microfluidic liver–kidney model to demonstrate the nephrotoxic responses to the hepatic metabolite of ifosfamide.\textsuperscript{43}

**USE OF MICROPHYSIOLOGICAL SYSTEMS TO SUPPORT PBPK MODELING AND PREDICTIONS OF DRUG DISPOSITION AND DRUG–DRUG INTERACTIONS**

Drug models to address how individual intrinsic and extrinsic factors affect the PK and PD of drugs are routinely developed. For example, to address potential and severity of DDIs, various \textit{in vitro}, \textit{in vivo}, and \textit{in silico} models are used.\textsuperscript{44–47} PBPK models have been increasingly developed and used to address DDI in regulatory submissions\textsuperscript{5,48} and published literature\textsuperscript{49} (Figure 3).

The key parameters required to build a reliable PBPK model for a drug include, in addition to a good system model, determination of the absorption, distribution, metabolism, and excretion (ADME) characteristics for the drug: absorption kinetics (rate and extent), distribution parameters (organ partitioning, and perfusion vs. permeability limitations), metabolism (in drug eliminating organs, such as the liver), and excretion (by the kidneys and into the bile). Microphysiological systems hold unique promise in providing a refined tool to establish these parameters that form the foundation of PBPK model development and DDI predictions. In the following section, the potential of different organ-on-a-chip approaches in providing critical ADME values for PBPK model development is reviewed. An overall schematic of a basic PBPK model and how microphysiological systems may fit into populating the drug properties in such models are shown in Figure 4.

**Absorption**

At present, the absorption characteristics of many drugs are not well defined, and modeling the extent and rate of absorption is often confounded by low confidence in parameter estimates for drug absorption. This is largely due to the lack of data on absolute bioavailability due to absence of PK information after intravenous administration of the drug or interest, and the confounding effects of distribution kinetics in modeling rate of absorption. Current static cell models to evaluate intestinal absorption, such as Caco-2 cells, are predominantly useful for determining the passive permeability values for a compound of interest and for identifying potential efflux and uptake transporters contributing to the absorption kinetics of the drug. However, predicting the ultimate rate and extent of absorption \textit{in vivo} in humans from \textit{in vitro} systems remains a considerable challenge due to the complex physiology of the human intestine and the processes involved in drug absorption from the gastrointestinal tract.

Current 2-D \textit{in vitro} models suffer from the lack of flow on either side of the cell system, generating an artificially
static system to define drug absorption that lacks any dynamic concentration gradients and flow dynamics observed in the human gastrointestinal tract. The microphysiological systems offer great promise in regenerating the microenvironment of the human gut, including the mechanical, absorptive (passive and active), and flow characteristics. For example, the gut-on-a-chip system that encompasses Caco-2 cells with epithelial cells layered between two microfluidic channels incorporates fluid flow on both sides of the Caco-2 cells, which mimic the shear stress and dynamics of the human intestine. This system incorporates spontaneous formation of microvilli and a polarized epithelium that seems to mimic the human intestine better than static (2-D) Caco-2 models. A weakness of this model, among other intestinal microphysiological systems, is that it uses Caco-2 cells, which are known to lack expression of critical intestinal metabolic enzymes, such as cytochrome P450 (CYP)3A4, that decrease drug bioavailability. Therefore, evaluation of intestinal first pass metabolism seems limited using this system. Nevertheless, this system was shown to have excellent epithelial integrity based on transepithelial electrical resistance measurements, and the data suggest that the system has great potential in refining predictive parameters for the absorption characteristics of drugs. The proof-of-concept of determining intestinal permeability has been demonstrated by Gao et al. who used a microfluidic device with Caco-2 cells to evaluate the intestinal permeability of curcumin. Surprisingly, the permeability values obtained from the microphysiological system with Caco-2 cells resulted in consistently higher apparent permeability values than those obtained from conventional 2-D Caco-2 transwell studies. This may be due to the spontaneous formation of microvilli in the microphysiological system, which increases the effective surface area or other differences in the monolayer formed, or the presence of the unstirred water layer in the two systems. Yet this difference illustrates the need for more comprehensive studies of permeability values in microphysiological systems that can be used to establish how these values quantitatively scale to in vivo human PK modeling, and to populate PBPK models that simulate drug absorption.

An interesting aspect of some of the human gut microphysiological systems is that they allow coculture of human gut microbiome with the epithelial cells. Although no applications of this coculture system to drug metabolism and absorption have yet been published, one can envision that, in the future, this system will allow studies to extrapolate the contribution of gut microbiome to the absorption characteristics and enterohepatic recycling of xenobiotics.

**Distribution**

Current methods of modeling distribution of drugs into specific organs rely mainly on few mathematical models of predicting tissue partitioning ($K_p$) on extrapolating distribution characteristics from preclinical species via body-size-based interspecies scaling (allometric scaling), and on applying limited imaging data to distribution modeling. The distribution kinetics of many drugs are not...
metabolite of trimethylamine formed in the liver, would pass the BBB and be detected in the brain.\textsuperscript{56} It was subsequently confirmed that trimethylamine N-oxide crosses the BBB. This example demonstrates the opportunity to gather important information of the pharmacological and toxicological role of metabolites in an \textit{in vitro} system that has not been previously possible. This example also suggests that microphysiological systems that allow study of drug distribution across tight barriers, such as the BBB or blood–testis barrier, could, in the future, be used to characterize permeability-rate-limited drug distribution, an area that is very challenging in current PBPK modeling (Figure 4). However, the question remains on how to scale the kinetic values obtained in microphysiological systems to a whole organ, and proof-of-concept studies in this area are needed. Similarly, further research is needed to explore the possibilities to study transporter contribution to distribution kinetics, and DDIs that may affect distribution kinetics.

**Metabolism**

At present, well-established methods, such as human liver microsomes and 2-D cultured human hepatocytes, are used to predict metabolic clearance in humans and to populate the clearance parameters in PBPK models. In general, the value of these 2-D systems in predicting human metabolic drug clearance is well recognized. However, these systems typically allow evaluation of metabolic processes solely in the hepatocytes and do not provide information on how other liver cell types may influence drug clearance. In addition, it is well recognized that these systems do not provide good information of transporter-metabolism interplay that could be kinetically extrapolated to PBPK models. Microfluidic liver models or liver-on-a-chip may offer key advantages in this regard, especially when hepatic zona is observed. Indeed, a microphysiological liver model that includes the four main liver cell types (hepatocytes, Kupffer cells, stellate cells, and endothelial cells) in a ratio mimicking the human liver has been reported.\textsuperscript{52} Relevant to ADME characterization and PBPK modeling, this system was shown to be viable for 28 days and have metabolic functions similar to the human liver as measured by metabolism of diclofenac, phenolphthalein, ethoxyresorufin, and testosterone metabolism. In contrast, some of the other liver chip models that have been explored up to date have suffered from the fact that they have used HepG2 cells, which do not have the complement of metabolic enzymes and metabolic capacity that is commonly observed in an adult human liver.

In the context of human clearance predictions and PBPK modeling, liver microphysiological systems that incorporate human hepatocytes have been shown to maintain the expression and activity of main drug metabolizing enzymes, and the data generated from these systems have been used to predict human \textit{in vivo} metabolic clearance.\textsuperscript{56,57} Although the quantitative predictive value of liver chips for estimating \textit{in vivo} clearance needs further validation, these methods clearly show that microphysiological systems that incorporate hepatocyte culture with flow offer a promising system to predict both the \textit{in vivo} metabolic clearance of drugs and
the interindividual variability of drug clearance. For example, the data collected for lidocaine clearance in a liver microphysiological system were successfully used to populate a PBPK model of lidocaine disposition in vivo. However, as of now, no in vitro model to generate appropriate predictions of renal clearance and renal transporter conditions that incorporate two fluid flow compartments that mimic the processes observed in the human kidneys are needed to improve the validity of kidney PBPK models and to populate PBPK models. This approach has many weaknesses, and, therefore, better in vitro models that closely mimic the processes observed in the human kidneys are needed to improve the validity of kidney PBPK models and predictions of renal clearance and renal transporter contribution to renal clearance. The kidney-on-a-chip system that incorporates two fluid flow compartments that mimic the blood and tubular lumen in the kidneys separated by the layer of tubular cells may be the best experimental model to generate appropriate in vitro values for predicting and modeling renal clearance. However, as of now, no studies have applied the kidney chip to human renal clearance modeling and predictions. In addition, the anatomic complexity of the kidneys and how the complexity impacts function is a significant and ongoing challenge to recapitulate in a microphysiological system. A "tubule" on a chip is not representative of a "kidney" on a chip.

**Excretion**

At present, there are no good static systems to predict renal clearance due to the complex physiology of the kidney and the generation of concentration gradients and pH gradients in the kidneys during passive reabsorption of drugs and water from tubular lumen. Passive permeability measures from Caco-2 or Manine-Darby canine kidney (MDCK) cells are generally used to estimate and predict reabsorption clearance in the kidneys and can be used to populate PBPK models. This approach has many weaknesses, and, therefore, better in vitro models that closely mimic the processes observed in the human kidneys are needed to improve the validity of kidney PBPK models and predictions of renal clearance and renal transporter contribution to renal clearance. The kidney-on-a-chip system that incorporates two fluid flow compartments that mimic the blood and tubular lumen in the kidneys separated by the layer of tubular cells may be the best experimental model to generate appropriate in vitro values for predicting and modeling renal clearance.

**What is in the future for microphysiological systems and PBPK modeling?**

The current state-of-the-art for gut chips is the use of Caco-2 cells. The next steps for the field may involve the use of cryopreserved human enterocytes in the microphysiological systems that would allow simultaneous assessment of the metabolic capacity and permeability in the intestine. If such systems could provide reliable predictive information of bioavailability ($F_a$ and $F_e$) as well as rate of absorption, the values generated would be of great advantage to PBPK modeling efforts. It is likely that intestinal chip systems in the future will allow evaluation of DDIs involving intestinal uptake and efflux transporters in the presence of flow. Such data would provide critical improvements to parameter inputs for PBPK modeling.

The microphysiological systems involving human liver cells, such as hepatocytes, have the great advantage of living for relatively long periods in culture, which is of importance in preclinical assessment of DDI potential. A major issue with current hepatocyte systems is their short lifetime in culture (72–96 hours), which typically limits studies of enzyme activity under steady-state conditions because of the apparent long half-lives of metabolic enzymes. As such, most induction evaluations are currently based on mRNA changes. Microphysiological systems that allow studies over several weeks hold great promise in generating predictive values of induction, downregulation, and time-dependent/irreversible inhibition of CYP enzymes. Long-term cultures would presumably allow assessment of homeostatic processes that may contribute to interplay between regulation of metabolic enzyme expression and direct modulation of their activity. In addition, long-term microphysiological systems will enable pulse-chase types of studies that may finally provide the CYP enzyme half-life estimates that are critical for PBPK model development.

Recent advances in human transporter biology have greatly improved our understanding of transporters’ role in drug PK and PD. Although transporter involvement in DDIs, drug disposition, and drug effects has been increasingly recognized, critical issues remain that need to be addressed to comprehensively evaluate DDI mechanisms, including metabolic enzyme-transporter interplay. In this area, microphysiological systems hold great promise to provide a novel platform to assess not only transported function and activity but also the impact of transporters on tissue drug accumulation.

**CONCLUSIONS**

Contemporary clinical pharmacology reviews of new drug submissions critically address key questions related to the safe and effective use of new drugs in individual patients with varying intrinsic and extrinsic factors. Appropriate applications of the state-of-the-art in vitro, in vivo, and in silico models (including the disease-drug trial models) are critical in drug development and regulatory review. With advances in the microphysiological system (organ-on-a-chip) technology, we will likely see more integration with model-informed drug development approaches for better understanding of disease, predicting drug effects, designing clinical trials, and, ultimately, better individualized patient treatment.

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