I J C R M
International Journal of Contemporary Research In Multidisciplinary

Review Article

Organ-on-a-Chip Technology for Drug Toxicity Prediction and Preclinical Evaluation: A Review

Pranjal Dinesh Ambade [1]*, Radhika Pradip Sahare [2], Achal Pandurang Misal [3], Mitali Ulhas Chopade [4], Kiran Dilip Gorade [4], Anisha Ashish Lohiya [5], Vaishnavi Ravindra Anpan [6], Vaibhav Santosh Shikare [7]

[1] Diploma in Pharmacy (D. Pharm), Datta Meghe College of Pharmacy, Wardha, Maharashtra, India
[2] Bachelor of Pharmacy (B. Pharm), Tulsakar College of Pharmacy, Hinganghat, Maharashtra, India
[3] Bachelor of Pharmacy (B. Pharm), Agnihotri College of Pharmacy, Wardha, Maharashtra, India
[4,6] Bachelor of Pharmacy (B. Pharm), Shree Sant Gajanan Maharaj College of Pharmacy, Buldhana, Maharashtra, India
[5] Master of Pharmacy (M. Pharm), Gurudatta Shikshan Prasarak Sanstha's Institute of Pharmacy, Akola, Maharashtra, India
[7] Assistant Professor, Department of Pharmaceutical Quality Assurance, Dr. Babasaheb Ambedkar Technological University (DBATU), Maharashtra, India

Corresponding Author: * Pranjal Dinesh Ambade

DOI: https://doi.org/10.5281/zenodo.24073849

Abstract

One of the biggest issues facing the pharmaceutical business is the high attrition rate in medication development, which is mostly caused by unexpected toxicity and lack of efficacy in people. Animal research and two-dimensional cell cultures are the mainstays of conventional preclinical evaluation, and both have established limitations in terms of forecasting human reactions. Organ-on-a-chip (OoC) technology, also known as microphysiological systems (MPS), replicates important structural and functional characteristics of human organs in vitro under regulated fluid flow and mechanical inputs by combining microfluidics, tissue engineering, and human-derived cells. The purpose of OoC platforms, their design concepts, and the primary organ models (liver, kidney, lung, gut, heart, brain, and bone marrow) utilized for toxicity assessment are all summarized in this article. The current regulatory environment, multi-organ and body-on-a-chip systems for pharmacokinetic and toxicokinetic research, and the technological and standardization issues that continue to impede widespread implementation are then covered. OoC models can identify human-relevant toxicities that animal models overlook, according to available data. However, before they can take the place of animal testing in regulatory decision-making, they must undergo more extensive validation, repeatability, and qualification for a specific context of usage.

Manuscript Information

- **ISSN No:** 2583-7397
- **Received:** 11-08-2026
- **Accepted:** 02-11-2026
- **Published:** 07-11-2026
- **IJCRM:**5(6); 2026: 113-121
- **©2026, All Rights Reserved**
- **Plagiarism Checked:** Yes
- **Peer Review Process:** Yes

How to Cite this Article

Ambade P D, Sahare R P, Misal A P, Chopade M U, Gorade K D, Lohiya A A, Anpan V R, Shikare V. Organ-on-a-Chip Technology for Drug Toxicity Prediction and Preclinical Evaluation: A Review. Int J Contemp Res Multidiscip. 2026;5(6):113-121.

Access this Article Online

www.multiarticlesjournal.com

© 2026 Pranjal Dinesh Ambade, Radhika Pradip Sahare, Achal Pandurang Misal, Mitali Ulhas Chopade, Kiran Dilip Gorade, Anisha Ashish Lohiya, Vaishnavi Ravindra Anpan, Vaibhav Santosh Shikare. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY NC ND). https://creativecommons.org/licenses/by-nc-nd/4.0/

KEYWORDS: Microphysiological systems, organ-on-a-chip, drug toxicity, preclinical assessment, microfluidics, Liver-Chip, body-on-a-chip, and novel approaches.

1. INTRODUCTION

The process of launching a new medication is lengthy, financially burdensome, and fraught with risk. Evaluations of pipelines from prominent pharmaceutical corporations reveal that a considerable fraction of candidate failures throughout development stems from safety and toxicity apprehensions, in addition to inadequate efficacy.[1,2] A commonly acknowledged analysis assessed that about 90% of clinical medication development does not succeed, with systemic toxicity and lack of efficacy as major factors.[3] The likelihood of approval fluctuates by therapeutic category and phase, although the overall probability for compounds advancing to phase I is still low.[6]Animal experimentation is the established basis for evaluating safety in humans. Nonetheless, the agreement between toxic effects reported in animals and those in people is constrained. A review of 150 chemicals revealed that animal research anticipated a substantial majority, but not every, human toxicity, highlighting significant omissions for certain organ systems [4]. Disparities in metabolism, transporter expression, immunological functionality, and receptor biology between species further compromise external validity [5]. Traditional two-dimensional monolayer preparations lack tissue architecture, mechanical stresses, perfusion, and multicellular interactions, causing primary hepatocytes and related cells to quickly forfeit their specialized function in such systems.

The advent of organ-on-a-chip technology was initiated to bridge this void. An OoC refers to a microfluidic culture system, generally made from transparent polymers such as polydimethylsiloxane (PDMS), that encompasses living human cells structured to emulate the tissue–tissue interactions and microenvironment of an organ. The discipline was invigorated by the lung-on-a-chip developed by Huh and his team, which emulated breathing-like cyclic tension at the alveolar-capillary junction [8]. Following that period, OoCs have been established for nearly all principal organs and are being more often employed in disease modeling, therapeutic efficacy evaluation, and safety pharmacology [9,10]. Wikswo elucidated the vast potential of these microphysiological systems within biology and medicine, functioning as links between in vitro tests and clinical research [11].Regulatory viewpoints are evolving. The FDA Modernization Act 2.0, passed in December 2022 in the United States, abolished the legal stipulation that required animal testing for drug applications and specifically endorsed non-animal techniques like as cell-based assays and microphysiological systems.[12] In April 2025, the FDA disclosed a plan to lessen and eventually eliminate animal testing obligations for monoclonal antibodies and various medications by employing novel techniques, including organ-on-chip systems.[13] These progressions render an essential, data-supported analysis of OoC toxicity opportune.This essay analyzes the core concepts of OoC design, significant organ-specific models for toxicity prediction, integration of many organs, validation and regulatory issues, and persistent obstacles.

2. Limitations of Conventional Preclinical Models

Table 1 compares the main preclinical model types used for toxicity evaluation. Each has a role in the drug development pipeline, but none alone recapitulates the human organ microenvironment together with scalable throughput.

Table 1. Comparison of conventional preclinical models and organ-on-a-chip systems for toxicity assessment

Feature	2D cell culture	3D spheroids/organoids	Animal models	Organ-on-a-chip
Human relevance	High if human cells, but dedifferentiation is common	High (human cells, self-organisation)	Limited by species differences [4,5]	High (human or iPSC-derived cells) [7,9]
Tissue architecture	Monolayer only	3D, but often lacks defined interfaces	Native, whole organism	Engineered tissue interfaces and compartments [7,8]
Fluid flow and mechanical forces	Absent	Mostly absent	Present	Controlled shear, stretch and perfusion [8,14]
Multi-organ interaction	None	Limited	Full, but non-human	Possible through fluidic coupling [43,46]
Real-time readouts	Endpoint assays	Mostly endpoint	Limited, invasive	Optical access, TEER, effluent sampling, integrated sensors [37]
Throughput and cost	High / low	Moderate	Low / high	Low to moderate; improving [15,16]
Main limitation	Poor physiological function	Variability, necrotic cores, limited vascularisation	Poor translation for some toxicities	Standardisation, scale-up, absorption of lipophilic compounds into PDMS [16,17]

3. Principles of Organ-on-a-Chip Design

3.1 Microfluidic architecture

The majority of OoCs utilize microchannels measuring from tens to hundreds of micrometers. A conventional two-channel configuration positions an epithelial or parenchymal cell layer alongside an endothelial layer on opposing sides of a slender permeable membrane, facilitating tissue–tissue communication, nutrition transfer, and the implementation of cyclic stretch or shear stress [7,8,14]. Perfusion delivers fresh medium and eliminates metabolites, resulting in steady-state exposures that more accurately reflect in vivo conditions compared to static dosing.

© 2026 Pranjal Dinesh Ambade, Radhika Pradip Sahare, Achal Pandurang Misal, Mitali Ulhas Chopade, Kiran Dilip Gorade, Anisha Ashish Lohiya. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY NC ND). https://creativecommons.org/licenses/by-nc-nd/4.0/

3.2 Materials

PDMS continues to be the predominant material due to its transparency, gas permeability, elasticity, and ease of molding; yet, it has the capacity to absorb minor hydrophobic compounds, complicating dose–response analysis. Options comprise thermoplastics (such as polystyrene and cyclic olefin copolymers), glass, and hydrogels, whereas contemporary platforms utilize 3D printing and materials with low absorption rates [17].

3.3 Cell sources

Outcomes of Cultures (OoCs) may utilize primary cells, immortalized cell lines, cells produced from induced pluripotent stem cells (iPSCs), and organoids. Cells produced from iPSCs provide patient-specific modeling and genetically varied panels, although the maturation state continues to be an issue [9,26]. Integrating organoids with microfluidic perfusion (organoids-on-chips) enhances nutrition distribution and consistency in comparison to traditional static organoid culture [18,19].

3.4 Sensing and readouts

Typical measurements encompass transepithelial/trans endothelial electrical resistance (TEER), permeability assays, immunofluorescence, secreted biomarkers (including albumin, urea, alanine aminotransferase, and cytokines), transcriptomics, and effluent mass spectrometry. Integrated electrochemical and optical sensors provide ongoing in situ assessment of oxygen levels, pH, and tissue functionality [20,21,37]. fundamental schematic of a dual-channel organ chip

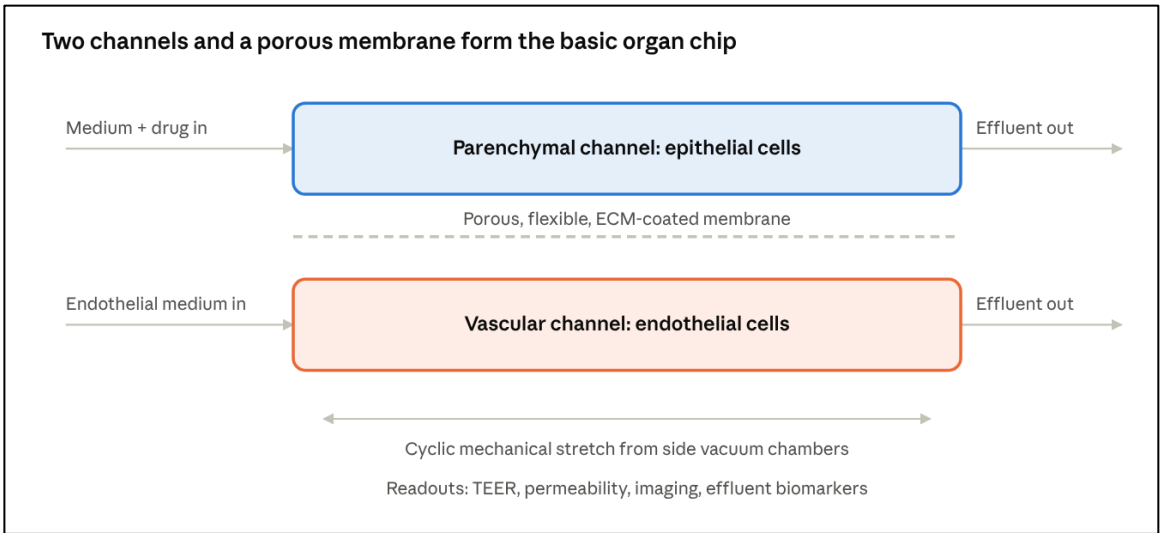


Figure 1. Schematic of a typical two-channel organ-on-a-chip: parenchymal (epithelial) and vascular (endothelial) channels separated by a porous, flexible membrane, with medium perfusion, drug dosing and effluent sampling.

4. Organ-Specific Models for Toxicity Prediction

4.1 Liver-on-a-chip

Drug-induced liver damage (DILI) is a primary factor in the cessation of drug development and the failure of clinical trials, while conventional hepatocyte monolayers rapidly lose cytochrome P450 functionality and polarity within a matter of days. Initial microfluidic liver models employed an endothelial-like barrier to replicate the sinusoidal structure and maintain hepatocyte functionality [20]. Real-time monitoring of metabolic activity in liver chips demonstrated that mitochondrial impairment induced by toxins may be dynamically observed [21].

A significant breakthrough was the Emulate Liver-Chip, which co-cultivates primary human hepatocytes alongside liver sinusoidal endothelial cells, Kupffer cells, and stellate cells in a flow environment. In a proof-of-concept investigation, it replicated human and interspecies toxicities of benchmark chemicals, such as bosentan-associated cholestatic damage, and demonstrated species-specific variations when comparing rat, canine, and human cells [22]. In an extensive blinded investigation involving 27 small molecules with established clinical hepatotoxicity profiles, the human Liver-Chip accurately detected 87% of drugs responsible for DILI in patients, despite having successfully undergone animal testing, achieving 100% specificity, while an economic assessment suggested that broader implementation in preclinical evaluations could yield significant productivity enhancements for the industry. These investigations represent some of the most robust quantitative data for OoC predictive toxicity, but the authors acknowledge the necessity for independent validation.

4.2 Kidney-on-a-chip

The proximal tubule serves as a primary location for drug-induced nephrotoxicity because to its elevated transporter expression and concentration capabilities. A human primary cell proximal tubule-on-a-chip subjected to physiological shear stress demonstrated enhanced cell polarization, albumin absorption, and glucose reabsorption, along with a more physiological reaction to cisplatin and cyclosporine A

© 2026 Pranjal Dinesh Ambade, Radhika Pradip Sahare, Achal Pandurang Misal, Mitali Ulhas Chopade, Kiran Dilip Gorade, Anisha Ashish Lohiya. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY NC ND). https://creativecommons.org/licenses/by-nc-nd/4.0/

compared to static culture. A microphysiological model of the proximal tubule has been delineated for the assessment of transporter activity and pharmacological interactions [25]. In the context of glomerular toxicity, iPSC-derived podocytes cultivated on-chip established a glomerular capillary wall that mimicked selective filtration and exhibited albuminuria in response to the chemotherapeutic agent adriamycin (doxorubicin) [26].

4.3 Lung-on-a-chip

The lung alveolus-on-a-chip implemented cyclic mechanical stress that simulates respiration [8]. Its application for toxicity was demonstrated in a model of drug-induced pulmonary edema, where interleukin-2 caused vascular permeability that was exacerbated by mechanical stress, and the TRPV4 ion channel was recognized as a potential therapeutic target [27]. A miniature airway-on-a-chip constructed from cells of COPD patients and healthy individuals facilitated the examination of inflammatory reactions to viral infections and cigaret smoke, as well as the impact of medications on these reactions. Lung chips have been utilized to discover antiviral agents for influenza and SARS-CoV-2 [29], as well as to simulate lung cancer proliferation and treatment efficacy [30].

4.4 Intestine-on-a-chip

The small intestine influences oral medication absorption and is a main target for gastrointestinal toxicity of anticancer medicines. The human gut-on-a-chip integrates Caco-2 cells with peristalsis-like movement and fluid dynamics, resulting in villus-like formations and improved barrier efficacy. Biopsy-derived organoid-based primary intestinal chips encompass many epithelial lineages and exhibit elevated levels of drug-metabolizing enzymes [32]. Anaerobic intestinal chips facilitate the study of intricate human microbiota, enabling the exploration of host-microbiome roles in drug metabolism and toxicity [33]. A colon-on-a-chip replicated the mucus layer and its related physiology [34].

4.5 Heart-on-a-chip

Cardiotoxicity, particularly arrhythmia resulting from hERG channel inhibition and contractile impairment, is a significant factor in medication attrition. Developed cardiac tissue chips featuring aligned muscle thin films facilitated the quantitative assessment of contractile stress in reaction to pharmacological substances [35]. Human iPSC-derived cardiomyocyte microphysiological systems equipped with integrated electrodes and perfusion yield metrics on beating rate, contractility, and electrophysiology for pharmacological assessment [36]. Platforms that incorporate many sensors, include liver and heart organoids, facilitated automated and continuous observation of medication reactions [37].

4.6 Blood–brain barrier and brain chips

The blood–brain barrier (BBB) restricts central nervous system exposure and also protects against neurotoxicants. Microfluidic blood-brain barrier models incorporating brain endothelial cells and astrocytes exhibit elevated transendothelial electrical resistance and enhanced physiological permeability compared to Transwell experiments [38]. A coupled neurovascular unit chip revealed metabolic coupling between endothelial and neuronal cells and drug-induced alterations, such as methamphetamine effects on neurovascular metabolism [39]. A hypoxia-augmented blood-brain barrier chip generated from iPSC-derived cells replicated efflux transporter functionality and antibody transport pertinent to biologic drug administration [40].

4.7 Bone marrow-on-a-chip

Myelosuppression is a common dose-restricting adverse effect of cytotoxic medications. A bone marrow-on-a-chip emulated hematopoietic niche functionality and preserved progenitor cells in vitro, demonstrating myelotoxic reactions to pharmaceuticals and radiation [41]. Subsequently, patient-derived chips simulated Shwachman–Diamond syndrome and the chemotherapy-related bone marrow toxicities, thereby endorsing individualized toxicity forecasting [42].

Table 2. Representative organ-on-a-chip models used for toxicity assessment

Organ	Key cell types	Example toxicity or drug readout	Reference
Liver	Primary hepatocytes, Kupffer, stellate and sinusoidal endothelial cells	Hepatotoxicity (DILI) prediction: 87% sensitivity, 100% specificity in a 27-drug study; species-specific toxicity	[22,23]
Kidney (proximal tubule)	Human renal proximal tubule epithelial cells	Cisplatin and cyclosporine A nephrotoxicity; transporter-mediated handling	[24,25]
Kidney (glomerulus)	iPSC-derived podocytes, glomerular endothelium	Adriamycin-induced albuminuria	[26]
Lung (alveolus)	Alveolar epithelium, lung microvascular endothelium	IL-2 induced pulmonary edema; TRPV4 as target	[8,27]
Lung (small airway)	Airway epithelium (healthy and COPD donors)	Inflammatory response to virus and smoke; drug effects	[28,29]
Intestine	Caco-2 or organoid-derived epithelium, endothelium, microbiota	Barrier function, drug metabolism, host–microbe interactions	[31–34]
Heart	iPSC-derived cardiomyocytes	Contractility, beat rate and electrophysiology changes	[35–37]
Blood–brain barrier	Brain microvascular endothelial cells, astrocytes, pericytes, neurons	Permeability, efflux and drug transport; neurovascular metabolism	[38–40]
Bone marrow	CD34+ haematopoietic cells, stromal cells	Myelosuppression after chemotherapy or irradiation	[41,42]

© 2026 Pranjal Dinesh Ambade, Radhika Pradip Sahare, Achal Pandurang Misal, Mitali Ulhas Chopade, Kiran Dilip Gorade, Anisha Ashish Lohiya. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY NC ND). https://creativecommons.org/licenses/by-nc-nd/4.0/

5. Multi-Organ and Body-on-a-Chip Systems

Numerous toxicities emerge from interactions between organs. A parent compound may undergo activation or detoxification in the liver, with the resultant metabolite potentially causing harm to the kidneys or heart. Multi-organ chips link separate organ modules via fluidic channels, enabling the circulation of metabolites and signaling molecules among tissues. Initial integrated systems amalgamated liver, heart, and lung tissue spheroids inside a unified recirculating system, exhibiting organ-specific reactions to pharmaceuticals like bleomycin [44]. A connected microphysiological system incorporating the colon, liver, kidney proximal tubule, blood-brain barrier, and skeletal muscle exhibited functional synergy, serving as a testing ground for systemic toxicity and pharmacokinetics [45].

A significant advancement in pharmacology is the implementation of fluidically linked, vascularized organ chips for quantitative in vitro-to-in vivo extrapolation (IVIVE). Herland et al. connected gut, liver, and kidney chips and employed computational pharmacokinetic modeling to forecast human pharmacokinetic parameters for medicines like nicotine and cisplatin [46]. Ronaldson-Bouchard and associates linked mature heart, liver, bone, and skin tissues originating from the same iPSC line through vascular flow, preserving tissue-specific characteristics for several weeks and facilitating patient-specific multi-organ investigations. Critiques of body-on-a-chip systems underscore persistent challenges in scaling (organ-to-organ size ratios), universal media, and concurrent maturation of various tissues [43,48].

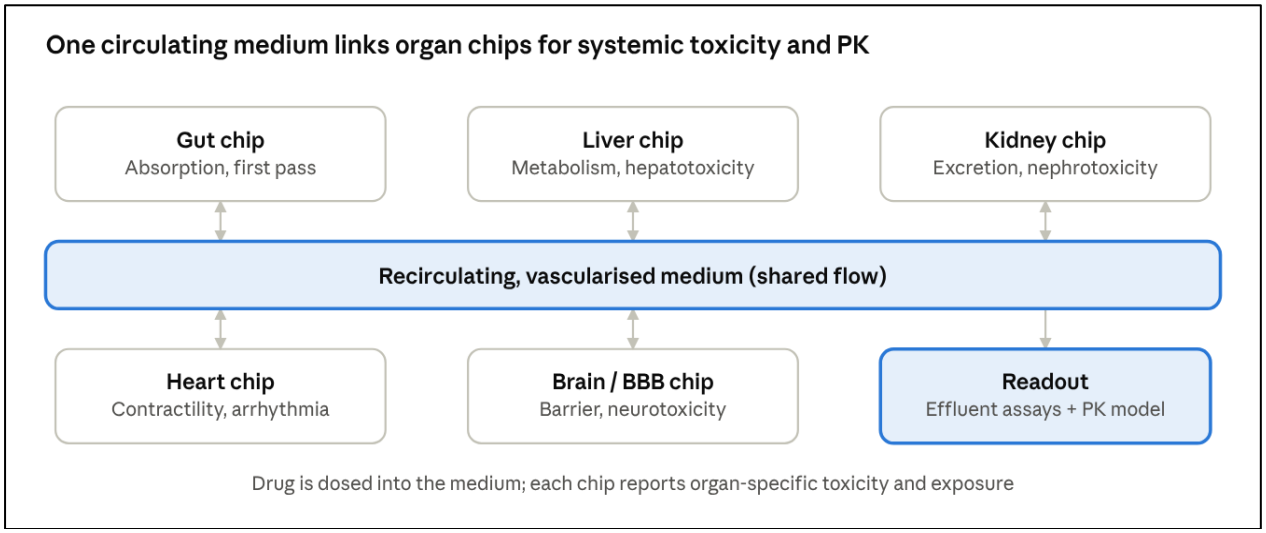


Figure 2. Conceptual body-on-a-chip: fluidically coupled liver, gut, kidney, heart and brain/BBB modules connected by a circulating, vascularised medium, with effluent analysis for pharmacokinetic and toxicokinetic modelling.

6. Validation, Regulatory Context and Industry Adoption

For an OoC to gain approval in regulatory filings, it must be validated for a specific context of usage, demonstrating reproducibility, benchmark substances, and explicit performance metrics. Fabre et al. proposed a paradigm for defining MPS concerning pharmaceutical safety and ADME applications, emphasizing purpose-oriented characterisation. [50]. [50]. [50]. A presentation including the FDA and the IQ Consortium MPS Affiliate focused on the evaluation and incorporation of complex in vitro models in drug development, highlighting the need for standardized performance metrics and reproducibility data across laboratories. [51]. Marx and colleagues articulated how biology-inspired MPS could improve patient outcomes and animal welfare, promoting a progressive, evidence-driven methodology for implementation. [49].

The FDA Modernisation Act 2.0 and the FDA's 2025 strategy to diminish animal testing for specific medication categories establish a legal and policy framework for increased adoption of non-animal techniques. Currently, OoC data are generally provided as supplemental or weight-of-evidence material in conjunction with conventional investigations, rather than as independent substitutes. Cost and productivity evaluations indicate that even a limited implementation, such as for preliminary hepatotoxicity risk mitigation, may prove advantageous [23]. Comprehensive evaluations of the discipline further highlight that amalgamation with computer modeling and artificial intelligence could enhance the predictive significance of OoC data [10,52].

7. Challenges and Future Perspectives

Table 3 lists the principal challenges for OoC toxicity testing and approaches under investigation.

Table 3. Key challenges in organ-on-a-chip toxicology and proposed solutions

Challenge	Description	Proposed approaches	Reference
Standardisation and reproducibility	Different chip designs, cell sources and protocols make cross-laboratory comparison	Reference compound sets, minimum reporting criteria, qualification for context	[49–51]

© 2026 Pranjal Dinesh Ambade, Radhika Pradip Sahare, Achal Pandurang Misal, Mitali Ulhas Chopade, Kiran Dilip Gorade, Anisha Ashish Lohiya. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY NC ND). https://creativecommons.org/licenses/by-nc-nd/4.0/

	hard	of use	
Compound absorption	PDMS adsorbs lipophilic small molecules, altering effective exposure	Low-absorption thermoplastics, surface coatings, measured concentrations in effluent	[15–17]
Cell maturity	iPSC-derived cells are often fetal-like, with limited metabolic capacity	Longer culture, mechanical and electrical conditioning, organoid integration	[9,18,47]
Throughput and scalability	Low number of chips per experiment; complex handling	Multiplexed plates, automation, higher-density formats	[10,16,52]
Multi-organ scaling	Physiological organ size ratios, shared medium, differing maturation times	Allometric scaling, PK modelling, vascularised coupling	[43,46,48]
Immune and microbiome components	Lack of full immune competence and microbiota in many models	Addition of immune cells, anaerobic co-culture	[28,33,53]
Regulatory acceptance	Need for validation data and agreed performance metrics	Public–private consortia, FDA–industry collaboration	[12,13,50,51]

Future progress is likely to depend on (i) integration of patient-derived iPSCs for population-level and personalised toxicity prediction, (ii) combining OoC data with physiologically based pharmacokinetic and machine-learning models, (iii) adoption of low-absorption, manufacturable materials, and (iv) large, multi-site validation studies with blinded compounds. As these phases progress, OoCs are most likely to complement, and selectively replace, animal studies for specific problems such as hepatotoxicity, barrier function and species-specific toxicity before expanding to the whole safety package.

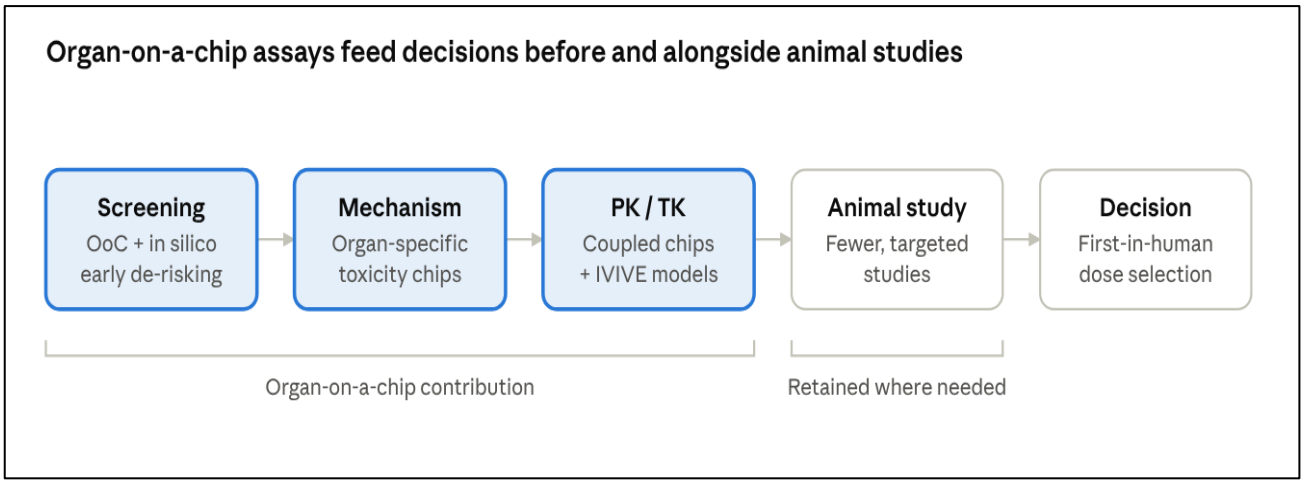


Figure 3. Proposed integration of organ-on-a-chip assays within the preclinical safety workflow: early screening, mechanistic toxicity studies, PK/toxicokinetic modelling and reduced, targeted animal studies leading to first-in-human dosing decisions.

8. CONCLUSION

Organ-on-a-chip technology offers human-relevant, mechanistically insightful systems for forecasting drug toxicity. Liver, kidney, lung, gut, heart, brain, and bone marrow chips have each demonstrated clinically significant toxicities, with the Liver-Chip findings suggesting that organ-on-chip systems may identify injuries overlooked by animal models. Multi-organ systems provide pharmacokinetic context. Nonetheless, standardization, material concerns, cell development, and regulatory validation persist as unresolved difficulties. Ongoing cooperation between academics, business, and regulatory bodies, along with meticulously crafted validation studies, will ascertain the extent to which organ-on-chip technologies might diminish dependence on animal testing and enhance the efficacy of preclinical assessments.

Conflict of Interest

The author declares no conflict of interest.

REFERENCES

1. Waring MJ, Arrowsmith J, Leach AR, Leeson PD, Mandrell S, Owen RM, et al. An analysis of the attrition of drug candidates from four major pharmaceutical companies. Nat Rev Drug Discov. 2015;14(7):475-86. doi:10.1038/nrd4609.
2. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov. 2004;3(8):711-6. doi:10.1038/nrd1470.
3. Sun D, Gao W, Hu H, Zhou S. Why 90% of clinical drug development fails and how to improve it? Acta Pharm Sin B. 2022;12(7):3049-62. doi:10.1016/j.apsb.2022.02.002.
4. Olson H, Betton G, Robinson D, Thomas K, Monro A, Kolaja G, et al. Concordance of the toxicity of pharmaceuticals in humans and in animals. Regul Toxicol Pharmacol. 2000;32(1):56-67. doi:10.1006/rtph.2000.1399.

© 2026 Pranjal Dinesh Ambade, Radhika Pradip Sahare, Achal Pandurang Misal, Mitali Ulhas Chopade, Kiran Dilip Gorade, Anisha Ashish Lohiya. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY NC ND). https://creativecommons.org/licenses/by-nc-nd/4.0/

5. Pound P, Ritskes-Hoitinga M. Is it possible to overcome issues of external validity in preclinical animal research? Why most animal models are bound to fail. J Transl Med. 2018;16(1):304. doi:10.1186/s12967-018-1678-1.
6. Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J. Clinical development success rates for investigational drugs. Nat Biotechnol. 2014;32(1):40-51. doi:10.1038/nbt.2786.
7. Bhatia SN, Ingber DE. Microfluidic organs-on-chips. Nat Biotechnol. 2014;32(8):760-72. doi:10.1038/nbt.2989.
8. Huh D, Matthews BD, Mammoto A, Montoya-Zavala M, Hsin HY, Ingber DE. Reconstituting organ-level lung functions on a chip. Science. 2010;328(5986):1662-8. doi:10.1126/science.1188302.
9. Ingber DE. Human organs-on-chips for disease modelling, drug development and personalized medicine. Nat Rev Genet. 2022;23(8):467-91. doi:10.1038/s41576-022-00466-9.
10. Low LA, Mummery C, Berridge BR, Austin CP, Tagle DA. Organs-on-chips: into the next decade. Nat Rev Drug Discov. 2021;20(5):345-61. doi:10.1038/s41573-020-0079-3.
11. Wikswo JP. The relevance and potential roles of microphysiological systems in biology and medicine. Exp Biol Med (Maywood). 2014;239(9):1061-72. doi:10.1177/1535370214542068.
12. United States Congress. FDA Modernization Act 2.0, S.5002, 117th Congress (2021-2022). Enacted as part of the Consolidated Appropriations Act, 2023, Public Law 117-328. Washington (DC): US Government; 2022.
13. US Food and Drug Administration. FDA announces plan to phase out animal testing requirement for monoclonal antibodies and other drugs [press release]. Silver Spring (MD): US Food and Drug Administration; 2025 Apr 10.
14. Esch EW, Bahinski A, Huh D. Organs-on-chips at the frontiers of drug discovery. Nat Rev Drug Discov. 2015;14(4):248-60. doi:10.1038/nrd4539.
15. Zhang B, Korolj A, Lai BFL, Radisic M. Advances in organ-on-a-chip engineering. Nat Rev Mater. 2018;3(8):257-78. doi:10.1038/s41578-018-0034-7.
16. Leung CM, de Haan P, Ronaldson-Bouchard K, Kim GA, Ko J, Rho HS, et al. A guide to the organ-on-a-chip. Nat Rev Methods Primers. 2022;2:33. doi:10.1038/s43586-022-00118-6.
17. Ahadian S, Civitarese R, Bannerman D, Mohammadi MH, Lu R, Wang E, et al. Organ-on-a-chip platforms: a convergence of advanced materials, cells, and microscale technologies. Adv Healthc Mater. 2018;7(2):1700506. doi:10.1002/adhm.201700506.
18. Park SE, Georgescu A, Huh D. Organoids-on-a-chip. Science. 2019;364(6444):960-5. doi:10.1126/science.aaw7894.
19. Skardal A, Shupe T, Atala A. Organoid-on-a-chip and body-on-a-chip systems for drug screening and disease modeling. Drug Discov Today. 2016;21(9):1399-411. doi:10.1016/j.drudis.2016.07.003.
20. Lee PJ, Hung PJ, Lee LP. An artificial liver sinusoid with a microfluidic endothelial-like barrier for primary hepatocyte culture. Biotechnol Bioeng. 2007;97(5):1340-6. doi:10.1002/bit.21360.
21. Bavli D, Prill S, Ezra E, Levy G, Cohen M, Vinken M, et al. Real-time monitoring of metabolic function in liver-on-chip microdevices tracks the dynamics of mitochondrial dysfunction. Proc Natl Acad Sci U S A. 2016;113(16):E2231-40. doi:10.1073/pnas.1522556113.
22. Jang KJ, Otieno MA, Ronxhi J, Lim HK, Ewart L, Kodella KR, et al. Reproducing human and cross-species drug toxicities using a Liver-Chip. Sci Transl Med. 2019;11(517):eaax5516. doi:10.1126/scitranslmed.aax5516.
23. Ewart L, Apostolou A, Briggs SA, Carman CV, Chaff JT, Heng AR, et al. Performance assessment and economic analysis of a human Liver-Chip for predictive toxicology. Commun Med (Lond). 2022;2:154. doi:10.1038/s43856-022-00209-1.
24. Jang KJ, Mehr AP, Hamilton GA, McPartlin LA, Chung S, Suh KY, et al. Human kidney proximal tubule-on-a-chip for drug transport and nephrotoxicity assessment. Integr Biol (Camb). 2013;5(9):1119-29. doi:10.1039/c3ib40049b.
25. Weber EJ, Chapron A, Chapron BD, Voellinger JL, Lidberg KA, Yeung CK, et al. Development of a microphysiological model of human kidney proximal tubule function. Kidney Int. 2016;90(3):627-37. doi:10.1016/j.kint.2016.06.011.
26. Musah S, Mammoto A, Ferrante TC, Jeanty SSF, Hirano-Kobayashi M, Mammoto T, et al. Mature induced-pluripotent-stem-cell-derived human podocytes reconstitute kidney glomerular-capillary-wall function on a chip. Nat Biomed Eng. 2017;1:0069. doi:10.1038/s41551-017-0069.
27. Huh D, Leslie DC, Matthews BD, Fraser JP, Jurek S, Hamilton GA, et al. A human disease model of drug toxicity-induced pulmonary edema in a lung-on-a-chip microdevice. Sci Transl Med. 2012;4(159):159ra147. doi:10.1126/scitranslmed.3004249.
28. Benam KH, Villenave R, Lucchesi C, Varone A, Hubeau C, Lee HH, et al. Small airway-on-a-chip enables analysis of human lung inflammation and drug responses in vitro. Nat Methods. 2016;13(2):151-7. doi:10.1038/nmeth.3697.

© 2026 Pranjal Dinesh Ambade, Radhika Pradip Sahare, Achal Pandurang Misal, Mitali Ulhas Chopade, Kiran Dilip Gorade, Anisha Ashish Lohiya. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY NC ND). https://creativecommons.org/licenses/by-nc-nd/4.0/

29. Si L, Bai H, Rodas M, Cao W, Oh CY, Jiang A, et al. A human-airway-on-a-chip for the rapid identification of candidate antiviral therapeutics and prophylactics. Nat Biomed Eng. 2021;5(8):815-29. doi:10.1038/s41551-021-00718-9.
30. Hassell BA, Goyal G, Lee E, Sontheimer-Phelps A, Levy O, Chen CS, et al. Human organ chip models recapitulate orthotopic lung cancer growth, therapeutic responses, and tumor dormancy in vitro. Cell Rep. 2017;21(2):508-16. doi:10.1016/j.celrep.2017.09.043.
31. Kim HJ, Huh D, Hamilton G, Ingber DE. Human gut-on-a-chip inhabited by microbial flora that experiences intestinal peristalsis-like motions and flow. Lab Chip. 2012;12(12):2165-74. doi:10.1039/c2lc40074j.
32. Kasendra M, Tovaglieri A, Sontheimer-Phelps A, Jalili-Firoozinezhad S, Bein A, Chalkiadaki A, et al. Development of a primary human small intestine-on-a-chip using biopsy-derived organoids. Sci Rep. 2018;8:2871. doi:10.1038/s41598-018-21201-7.
33. Jalili-Firoozinezhad S, Gazzaniga FS, Calamari EL, Camacho DM, Fadel CW, Bein A, et al. A complex human gut microbiome cultured in an anaerobic intestine-on-a-chip. Nat Biomed Eng. 2019;3(7):520-31. doi:10.1038/s41551-019-0397-0.
34. Sontheimer-Phelps A, Chou DB, Tovaglieri A, Ferrante TC, Duckworth T, Fadel C, et al. Human colon-on-a-chip enables continuous in vitro analysis of colon mucus layer accumulation and physiology. Cell Mol Gastroenterol Hepatol. 2020;9(3):507-26. doi:10.1016/j.jcmgh.2019.11.008.
35. Grosberg A, Alford PW, McCain ML, Parker KK. Ensembles of engineered cardiac tissues for physiological and pharmacological study: heart on a chip. Lab Chip. 2011;11(24):4165-73. doi:10.1039/c1lc20557a.
36. Mathur A, Loskill P, Shao K, Huebsch N, Hong S, Marcus SG, et al. Human iPSC-based cardiac microphysiological system for drug screening applications. Sci Rep. 2015;5:8883. doi:10.1038/srep08883.
37. Zhang YS, Aleman J, Shin SR, Kilic T, Kim D, Mousavi Shaegh SA, et al. Multisensor-integrated organs-on-chips platform for automated and continual in situ monitoring of organoid behaviors. Proc Natl Acad Sci U S A. 2017;114(12):E2293-302. doi:10.1073/pnas.1612906114.
38. Booth R, Kim H. Characterization of a microfluidic in vitro model of the blood-brain barrier (μBBB). Lab Chip. 2012;12(10):1784-92. doi:10.1039/c2lc40094d.
39. Maoz BM, Herland A, FitzGerald EA, Grevesse T, Vidoudez C, Pacheco AR, et al. A linked organ-on-chip model of the human neurovascular unit reveals the metabolic coupling of endothelial and neuronal cells. Nat Biotechnol. 2018;36(9):865-74. doi:10.1038/nbt.4226.
40. Park TE, Mustafaoglu N, Herland A, Hasselkus R, Mannix R, FitzGerald EA, et al. Hypoxia-enhanced blood-brain barrier chip recapitulates human barrier function and shuttling of drugs and antibodies. Nat Commun. 2019;10:2621. doi:10.1038/s41467-019-10588-0.
41. Torisawa YS, Spina CS, Mammoto T, Mammoto A, Weaver JC, Tat T, et al. Bone marrow-on-a-chip replicates hematopoietic niche physiology in vitro. Nat Methods. 2014;11(6):663-9. doi:10.1038/nmeth.2938.
42. Chou DB, Frismantas V, Milton Y, David R, Pop-Damkov P, Ferguson D, et al. On-chip recapitulation of clinical bone marrow toxicities and patient-specific pathophysiology. Nat Biomed Eng. 2020;4(4):394-406. doi:10.1038/s41551-019-0495-z.
43. Lee SH, Sung JH. Organ-on-a-chip technology for reproducing multiorgan physiology. Adv Healthc Mater. 2018;7(2):1700419. doi:10.1002/adhm.201700419.
44. Skardal A, Murphy SV, Devarasetty M, Mead I, Kang HW, Seol YJ, et al. Multi-tissue interactions in an integrated three-tissue organ-on-a-chip platform. Sci Rep. 2017;7:8837. doi:10.1038/s41598-017-08879-x.
45. Vernetti L, Gough A, Baetz N, Blutt S, Broughman JR, Brown JA, et al. Functional coupling of human microphysiology systems: intestine, liver, kidney proximal tubule, blood-brain barrier and skeletal muscle. Sci Rep. 2017;7:42296. doi:10.1038/srep42296.
46. Herland A, Maoz BM, Das D, Somayaji MR, Prantil-Baun R, Novak R, et al. Quantitative prediction of human pharmacokinetic responses to drugs via fluidically coupled vascularized organ chips. Nat Biomed Eng. 2020;4(4):421-36. doi:10.1038/s41551-019-0498-9.
47. Ronaldson-Bouchard K, Teles D, Yeager K, Tavakol DN, Zhao Y, Chramiec A, et al. A multi-organ chip with matured tissue niches linked by vascular flow. Nat Biomed Eng. 2022;6(4):351-71. doi:10.1038/s41551-022-00882-6.
48. Sung JH, Wang YI, Sriram NN, Jackson M, Long C, Hickman JJ, et al. Recent advances in body-on-a-chip systems. Anal Chem. 2019;91(1):330-51. doi:10.1021/acs.analchem.8b05293.
49. Marx U, Akabane T, Andersson TB, Baker E, Beilmann M, Beken S, et al. Biology-inspired microphysiological systems to advance patient benefit and animal welfare in drug development. ALTEX. 2020;37(3):365-94. doi:10.14573/altex.2001241.
50. Fabre K, Berridge B, Proctor WR, Ralston S, Will Y, Baran SW, et al. Introduction to a manuscript series on the characterization and use of microphysiological systems (MPS) in pharmaceutical safety and ADME applications.

© 2026 Pranjal Dinesh Ambade, Radhika Pradip Sahare, Achal Pandurang Misal, Mitali Ulhas Chopade, Kiran Dilip Gorade, Anisha Ashish Lohiya. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY NC ND). https://creativecommons.org/licenses/by-nc-nd/4.0/

51. Lab Chip. 2020;20(6):1049-57. doi:10.1039/c9lc01168d.
52. Baran SW, Brown PC, Baudy AR, Fitzpatrick SC, Frantz C, Fullerton A, et al. Perspectives on the evaluation and adoption of complex in vitro models in drug development: workshop with the FDA and the pharmaceutical industry (IQ MPS Affiliate). ALTEX. 2022;39(2):297-314. doi:10.14573/altex.2112203.
53. Ma C, Peng Y, Li H, Chen W. Organ-on-a-chip: a new paradigm for drug development. Trends Pharmacol Sci. 2021;42(2):119-33. doi:10.1016/j.tips.2020.11.009.
54. Wu Q, Liu J, Wang X, Feng L, Wu J, Zhu X, et al. Organ-on-a-chip: recent breakthroughs and future prospects. Biomed Eng Online. 2020;19(1):9. doi:10.1186/s12938-020-0752-0.

Creative Commons (CC) License

This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution–Non-Commercial–No Derivatives 4.0 International (CC BY-NC-ND 4.0) license. This license permits sharing and redistribution of the article in any medium or format for non-commercial purposes only, provided that appropriate credit is given to the original author(s) and source. No modifications, adaptations, or derivative works are permitted under this license.



Pranjal Dinesh Ambade is a Diploma in Pharmacy (D.Pharm) student at Datta Meghe College of Pharmacy, Wardha, Maharashtra, India. His academic interests include pharmaceutical sciences, drug formulation, and emerging developments in pharmaceutical research.



Radhika Pradip Sahare is a Bachelor of Pharmacy (B.Pharm) student at Tulsakar College of Pharmacy, Hinganghat, Maharashtra, India. Her academic interests include pharmaceutical sciences, formulation development, and drug delivery systems.



Achal Pandurang Misal is a Bachelor of Pharmacy (B.Pharm) student at Agnihotri College of Pharmacy, Wardha, Maharashtra, India. His academic interests include pharmaceutical research, formulation development, and pharmaceutical technology.



Mitali Ulhas Chopade is a Bachelor of Pharmacy (B.Pharm) student at Shree Sant Gajanan Maharaj College of Pharmacy, Buldhana, Maharashtra, India. Her academic interests include pharmaceutical sciences, drug formulation, and pharmaceutical research.



Kiran Dilip Gorade is a Bachelor of Pharmacy (B.Pharm) student at Shree Sant Gajanan Maharaj College of Pharmacy, Buldhana, Maharashtra, India. His academic interests include pharmaceutical formulation, pharmaceutical analysis, and advancements in drug delivery systems.



Anisha Ashish Lohiya is a Master of Pharmacy (M.Pharm) student at Gurudatta Shikshan Prasarak Sanstha's Institute of Pharmacy, Akola, Maharashtra, India. Her academic interests include pharmaceutical research, formulation development, quality assurance, and novel drug delivery systems.



Vaishnavi Ravindra Anpan is a Bachelor of Pharmacy (B.Pharm) student at Shree Sant Gajanan Maharaj College of Pharmacy, Buldhana, Maharashtra, India. Her academic interests include pharmaceutical sciences, research methodology, formulation development, and emerging pharmaceutical technologies.



Vaibhav Santosh Shikare is an Assistant Professor in Pharmaceutical Quality Assurance at Dr. Babasaheb Ambedkar Technological University, Maharashtra, India. He holds an M.pharm degree. His research interests include analytical method development, HPLC/RP-HPLC, herbal and novel drug delivery, and AI applications in pharmaceutical sciences. He founded Pharmabuddy Writing Services and contributes to scientific writing and peer review.

© 2026 Pranjal Dinesh Ambade, Radhika Pradip Sahare, Achal Pandurang Misal, Mitali Ulhas Chopade, Kiran Dilip Gorade, Anisha Ashish Lohiya. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC BY NC ND). https://creativecommons.org/licenses/by-nc-nd/4.0/