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(REVIEW ARTICLE)

From mice to microchips: Organ-on-a-chip technology as a paradigm shift in drug discovery, disease modeling, and personalized medicine

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Abstract

Organ-on-a-chip (OoC) technology is an interdisciplinary platform that combines microfluidics, micro-electromechanical systems, tissue engineering, and human cell biology to recapitulate the structural and physiological complexity of native human organs within centimetre-scale microdevices. The persistent failure of conventional two-dimensional cell culture and animal models to predict human drug responses—reflected in clinical attrition rates exceeding ninety percent—has driven urgent demand for more predictive in vitro systems. OoC platforms address this gap by reconstituting functional tissue–tissue interfaces such as the alveolar–capillary unit, hepatic sinusoid, renal proximal tubule, intestinal villus, and blood–brain barrier within perfused microchannels exposed to physiologically relevant mechanical cues including cyclic strain, shear stress, and electrical pacing. This review provides a comprehensive account of the architecture, working principles, fabrication strategies, and pharmaceutical applications of OoC systems. Detailed mechanistic descriptions of lung-, liver-, heart-, kidney-, gut-, blood–brain barrier-, skin-, and tumour-on-a-chip models are presented, along with multi-organ body-on-a-chip platforms enabling integrated pharmacokinetic–pharmacodynamic studies. The commercial landscape (Emulate, MIMETAS, TissUse, CN Bio, Hesperos), regulatory milestones including the United States Food and Drug Administration Modernization Act 2.0 (2022) and FDA acceptance of Liver-Chip data in investigational new drug applications, and challenges relating to standardization, polydimethylsiloxane-mediated drug absorption, vascularization, and scale-up are critically discussed. Integration with induced pluripotent stem cells, artificial intelligence, and multi-omics technologies positions organ-on-a-chip as a cornerstone of New Approach Methodologies and the future of precision pharmaceutical research.

Keywords: Organ-on-a-chip; Microphysiological systems; Microfluidics; Drug discovery; Personalized medicine; New Approach Methodologies

1. Introduction

The pharmaceutical industry continues to grapple with one of the most expensive productivity crises in modern science. Bringing a single new drug to market now exceeds USD 2.6 billion, requires more than a decade of development, and is associated with an overall clinical attrition rate of approximately ninety percent between Phase I trials and regulatory approval [1,2]. Failures at late stages are most commonly attributable to lack of efficacy and unanticipated toxicity—particularly hepatotoxicity, cardiotoxicity and nephrotoxicity—that are not detected by preclinical models [3]. These failures point to a fundamental translational deficiency in the predictive value of the in vitro and in vivo systems on which modern drug discovery still rests.

Two preclinical paradigms have dominated the past century. Two-dimensional (2D) monolayer cell culture is inexpensive, scalable, and amenable to high-throughput screening, but it lacks the three-dimensional architecture,

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mechanical forces, fluid flow, paracrine signalling, and tissue–tissue interfaces that govern organ physiology in vivo [4]. Animal models—principally rodents, dogs and non-human primates—provide systemic complexity but frequently fail to predict human responses because of species-specific differences in drug metabolism, target expression, immune function, and disease pathophysiology. The historical concordance of animal toxicity studies with human adverse events is only about seventy-one percent across organ systems, and below fifty percent for important toxicities such as hepatotoxicity and cutaneous reactions [5]. Beyond predictive limitations, animal experimentation is increasingly constrained by ethical, regulatory, and economic considerations, culminating in the 2022 United States FDA Modernization Act 2.0, which removed the statutory requirement for animal testing in new drug applications [6].

Organ-on-a-chip (OoC) technology—also referred to as microphysiological systems (MPS)—has emerged as a transformative response to these challenges [7]. An organ-on-a-chip is a microengineered cell-culture device, typically a few square centimetres in size, in which living human cells are arranged within perfused microchannels in geometric configurations that reproduce the smallest functional unit of an organ. By imposing controlled mechanical strain, fluid shear, electrical pacing, and biochemical gradients on the cultured tissue, these devices recreate organ-level functions that are absent from conventional cultures [8,9]. The seminal lung-on-a-chip reported by Huh and colleagues in 2010 demonstrated, for the first time, that an in vitro device could reproduce the cyclic distension of the alveolar–capillary interface, the trans-epithelial movement of nanoparticles, and a physiologically relevant inflammatory response to bacterial challenge [10]. Since that breakthrough—catalysed in part by the DARPA and NIH Microphysiological Systems programmes launched in 2012 [11]—OoC technology has progressed from single-organ proofs of concept into commercial platforms, multi-organ body-on-a-chip systems, and the recently endorsed New Approach Methodologies (NAMs) framework adopted by regulatory agencies worldwide [12].

The objective of this review is to provide a comprehensive, mechanistically detailed account of organ-on-a-chip systems for pharmaceutical scientists, biomedical engineers, and translational researchers. The architecture and working principles are described in depth; fabrication technologies, organ-specific designs, multi-organ integration, applications in drug discovery and personalized medicine, the commercial and regulatory landscape, and the remaining challenges and future directions are then discussed.

2. Methodology

This narrative review was prepared through a structured literature search across PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and Google Scholar covering publications from January 2000 through October 2025. The search strategy combined the terms "organ-on-a-chip," "organ-on-chip," "microphysiological system," and "body-on-a-chip" with secondary terms relating to drug discovery, toxicity, disease modelling, personalized medicine, and pharmacokinetics. Organ-specific searches were performed for each model discussed. Regulatory documents from the United States Food and Drug Administration, European Medicines Agency, and National Institutes of Health were also consulted. Peer-reviewed primary research articles, reviews, and regulatory white papers in the English language were included; conference abstracts, non-peer-reviewed preprints, and theses were excluded except where they represented seminal contributions. Particular emphasis was placed on landmark studies establishing each organ-specific platform and on recent (2020–2025) literature describing commercial translation and regulatory acceptance.

3. Architecture and Working Principles of Organ-on-a-Chip Systems

Although designs vary widely, virtually all organ-on-a-chip systems share five architectural elements: one or more microfluidic channels containing the relevant cell populations, a biocompatible substrate supporting three-dimensional tissue organization, perfusion machinery providing continuous fluid flow, actuators that deliver organ-specific mechanical or electrical cues, and integrated or modular readouts for real-time measurement of cellular function. Each is summarized below.

Table 1 Comparison of conventional preclinical models with organ-on-a-chip platforms.

Parameter	2D culture	3D organoid	Animal model	Organ-on-a-chip
Human physiological relevance	Low	Moderate	Moderate (species-divergent)	High
Tissue–tissue interfaces	Absent	Limited	Present	Reconstituted

Mechanical cues (strain, shear)	Absent	Limited	Present	Controlled and tunable
Perfusion / fluid flow	Static	Mostly static	Systemic	Continuous, microfluidic
Real-time longitudinal readouts	Endpoint only	Limited	Difficult	Integrated biosensors
Patient-specific (iPSC compatible)	Limited fidelity	Yes	No	Yes (high fidelity)
Predictive accuracy (human ADME/Tox)	Low	Moderate	≈50–70%	>85% (validated assays)
Ethical concerns	Minimal	Minimal	High	Minimal

3.1. Microfluidic channels and biomaterials

The functional core of an OoC device is one or more microchannels with dimensions of 100 μm to 1 mm. These channels are sized to approximate physiological capillary diameters and to maintain laminar flow (Reynolds number << 1), permitting precise control over chemical gradients, shear stress, and residence times [13]. Most contemporary devices employ a two-channel architecture in which an upper parenchymal channel containing the organ-specific epithelium is separated from a lower vascular channel lined with endothelial cells by a thin porous membrane (~10 μm thick, 0.4–8 μm pores). Polydimethylsiloxane (PDMS) is the dominant substrate because it is optically transparent, gas-permeable, biocompatible, and amenable to rapid prototyping; its principal limitation—absorption of hydrophobic small molecules—is increasingly mitigated by thermoplastic alternatives (cyclic olefin copolymer, polystyrene) or glass-based devices for pharmacokinetic-grade work [14]. Membrane surfaces are functionalized with extracellular matrix proteins such as collagen, fibronectin, or laminin to support cell attachment and polarization, and three-dimensional hydrogel compartments (collagen, fibrin, GelMA, decellularized matrix) provide tissue-specific biochemical and mechanical cues.

3.2. Cellular components and microenvironment

OoC devices accommodate primary human cells, immortalized cell lines (Caco-2, HepG2, hCMEC/D3), and—increasingly—human induced pluripotent stem cell (iPSC)-derived lineages such as cardiomyocytes, hepatocyte-like cells, brain microvascular endothelial cells, and podocytes [15]. Co-culture of parenchymal cells with endothelium, immune cells, stromal fibroblasts, and commensal microbiota is essential for recapitulating tissue-level physiology. A defining feature of OoC technology is the controlled imposition of organ-specific biomechanical cues: cyclic uniaxial strain (5–15%) at physiological frequencies (0.2–1 Hz) is used in lung, gut, and cardiovascular models to recapitulate breathing, peristalsis, and pulsatile flow; continuous perfusion generates well-defined fluid shear essential for endothelial polarization and hepatocyte function; electrical pacing drives functional maturation of cardiac and neural tissues; and laminar-flow biochemical gradients allow investigators to mimic zonation within the liver lobule or the anaerobic intestinal lumen [16].

3.3. Integrated sensors and readouts

Real-time monitoring distinguishes modern OoC platforms from conventional Transwell or organoid cultures. Integrated transepithelial electrical resistance (TEER) electrodes track barrier integrity at second-to-minute resolution. Microelectrode arrays record cardiac field potentials and neuronal activity. Optical sensors measure dissolved oxygen, pH, glucose, and lactate, while electrochemical aptamer- and antibody-based biosensors quantify cytokines, hormones, and drug metabolites within microliter sample volumes [17]. High-content imaging through optically transparent PDMS or glass enables longitudinal three-dimensional confocal imaging of tissue dynamics, and the convergence of these sensing modalities with machine-learning analysis is rapidly transforming OoC platforms into closed-loop autonomous experimentation systems.

4. Fabrication Technologies

Fabrication strategies balance resolution, throughput, cost, and biocompatibility. Soft lithography remains the workhorse of OoC fabrication: a master mould is generated by photolithography of SU-8 photoresist on a silicon wafer, and liquid PDMS prepolymer is poured over the master, cured, peeled off, and bonded to glass after oxygen-plasma activation [18]. The technique is rapid and inexpensive but does not scale economically to mass production. Three-

dimensional bioprinting—using extrusion, inkjet, or stereolithography—permits direct deposition of cell-laden bioinks in patient- or organ-specific geometries and is particularly valuable for vascularized tissue chips, where sacrificial templating with Pluronic F-127 or carbohydrate glass produces perfusable multi-scale vascular networks [19]. For commercial-scale, regulatory-grade manufacturing, injection moulding and hot embossing of thermoplastics provide tight dimensional tolerances and avoid PDMS-related drug absorption, and are the preferred route for industrial platforms such as MIMETAS OrganoPlate® and CN Bio PhysioMimix™. Laser micromachining and computer numerical control micromilling enable rapid prototyping of plastic and glass devices without lithographic masters, with femtosecond lasers capable of producing three-dimensional channel networks within bulk glass for fully optically accessible, drug-inert devices.

5. Organ-Specific Models: Architecture, Working Principles, and Applications

Each organ-on-a-chip platform is designed around the smallest functional unit of the target organ. The architecture, cellular composition, mechanical environment, and pharmaceutical applications of each major model are described below.

5.1. Lung-on-a-chip

The lung-on-a-chip was the first and remains the most extensively validated OoC platform [10]. The seminal design from Huh and colleagues consists of two parallel microchannels separated by a thin (10 μm), porous (0.4 μm pore size), flexible PDMS membrane. Primary human alveolar epithelial cells are cultured on the upper surface of the membrane at an air–liquid interface, while human pulmonary microvascular endothelial cells line its lower surface and are exposed to flowing culture medium that mimics the capillary compartment. Critically, two hollow side chambers flanking the central channel are connected to a computer-controlled vacuum source: cyclic application of negative pressure stretches the elastic membrane laterally by approximately ten percent strain at 0.2 Hz, faithfully reproducing the mechanical deformation of the alveolus during normal breathing [10].

This biomechanical environment yields several physiologically relevant behaviours that are absent from static culture: tight junction formation and barrier function comparable to native epithelium, surfactant production, and mechanically-modulated drug toxicity. In a landmark application, the chip reproduced interleukin-2–induced pulmonary oedema in vitro, including the characteristic vascular leak and reversal by angiopoietin-1 and a TRPV4 channel inhibitor that was subsequently advanced to clinical trials [20]. Small-airway-on-a-chip variants developed by Benam and colleagues recapitulate chronic obstructive pulmonary disease and asthma, including patient-derived mucociliary differentiation, smoking-induced inflammation, and viral exacerbation [21]. During the COVID-19 pandemic, alveolus chips populated with SARS-CoV-2–infected epithelium were used to demonstrate barrier disruption and to screen antiviral candidates including remdesivir, hydroxychloroquine (negative), and amodiaquine [22].

5.2. Liver-on-a-chip

Because the liver is the principal site of drug metabolism and the most common organ affected by drug-induced injury, the liver-on-a-chip has attracted intense pharmaceutical interest. The functional unit being modelled is the hepatic sinusoid: cords of polarized hepatocytes flanked by fenestrated sinusoidal endothelium, with Kupffer macrophages and hepatic stellate cells in the space of Disse. The dual-channel Emulate Liver-Chip places primary human hepatocytes in a 3D collagen sandwich in the upper channel, with liver sinusoidal endothelial cells, Kupffer cells, and stellate cells in the lower channel separated by a porous membrane. Continuous perfusion at a low shear rate provides oxygenation and metabolic clearance and maintains cytochrome P450 (CYP3A4, CYP2B6, CYP1A2) activity at near-physiological levels for two to four weeks, dramatically exceeding the 24–72 hour functional window of conventional hepatocyte monolayers [23].

Quantitative validation of the Liver-Chip platform is now well established. In a study by Ewart and colleagues encompassing 870 drug-induced liver injury (DILI) cases, the Emulate Liver-Chip detected hepatotoxicity for 87% of compounds that had been falsely classified as non-toxic by conventional 2D and animal models, with zero false positives, projecting an annual benefit of approximately USD 3 billion to the pharmaceutical industry through earlier failure of toxic candidates [14]. The platform also distinguishes species-specific toxicities and has been used to model hepatitis B and C infection, alcoholic and non-alcoholic steatohepatitis, and to predict species-divergent metabolism of bosentan, fialuridine, and acetaminophen.

5.3. Heart-on-a-chip

Cardiotoxicity—particularly QT prolongation and contractile dysfunction—is a leading cause of late-stage drug failure and post-marketing withdrawal. Heart-on-a-chip platforms combine iPSC-derived cardiomyocytes with electrical and mechanical readouts in physiologically structured tissues. A representative architecture, the biowire or cardiac microtissue chip, suspends a self-assembling three-dimensional cardiac bundle between two flexible PDMS micropillars; the pillars act as cantilevers whose deflection during each contraction is optically tracked and converted into contractile force, beat rate, and twitch kinetics, providing a non-invasive longitudinal mechanical readout [24].

A complementary architecture uses microelectrode arrays embedded beneath the cardiac tissue to record field potentials, action-potential duration, and conduction velocity. Electrical pacing at progressively increasing frequencies, combined with mechanical loading from the cantilevers, drives functional maturation of iPSC-derived cardiomyocytes toward an adult-like phenotype—aligned sarcomeres, increased T-tubule formation, oxidative metabolism, and positive force–frequency response—as reported by Ronaldson-Bouchard and colleagues in 2018 [25]. Heart-Chips have been used to detect doxorubicin-induced cardiotoxicity, terfenadine-induced QT prolongation, and to model inherited cardiomyopathies such as Barth syndrome using patient-derived iPSCs.

5.4. Kidney-on-a-chip

The kidney is a major site of drug clearance via active transport (organic anion and cation transporters, P-glycoprotein) and a frequent target of dose-limiting toxicity. The principal kidney-on-a-chip target is the proximal tubule. The classical design developed by Jang and colleagues consists of a porous polyester membrane separating an upper tubular lumen channel from a lower interstitial channel; primary human proximal tubule epithelial cells (PTECs) are seeded on the upper surface, and human renal microvascular endothelial cells line the underside [26]. The defining mechanical cue is luminal fluid shear stress of approximately 0.2 dyne cm^{-2}, which drives apical–basal polarization, enhanced expression of brush-border enzymes and aquaporins, and functional reconstitution of organic anion and cation transporters [26]. Under flow, PTEC monolayers achieve transepithelial resistances and albumin reabsorption rates that approach in vivo values. Glomerulus-on-a-chip variants developed by Musah and colleagues use iPSC-derived podocytes co-cultured with glomerular endothelial cells across a porous membrane, generating size-selective albumin filtration and demonstrating dose-dependent nephrotoxicity of doxorubicin [27]. Kidney chips have been used to predict cisplatin- and gentamicin-induced nephrotoxicity and to model autosomal-dominant polycystic kidney disease using patient iPSCs.

5.5. Gut-on-a-chip

The human gut presents an exceptional engineering challenge because it requires simultaneous accommodation of oxygenated host epithelium with three-dimensional villi, mechanical peristalsis, and an anaerobic microbial community of more than one thousand species. The gut-on-a-chip developed by Kim, Huh, and Ingber addresses these requirements with elegant simplicity [28]. The device employs the two-channel dual-vacuum-chamber architecture inherited from the lung-chip. Caco-2 cells, or alternatively primary intestinal organoid-derived epithelium, are cultured on a porous membrane and exposed to continuous luminal perfusion ($\sim$30 μL h^{-1}, $\sim$0.02 dyne cm^{-2} shear) and cyclic mechanical strain ($\sim$10% at 0.15 Hz) that mimics peristaltic motion [28,29].

Under these conditions, the flat Caco-2 monolayer spontaneously undergoes morphogenesis into 100–200 μm tall finger-like villi within five to seven days, accompanied by differentiation into all four major intestinal lineages: absorptive enterocytes, goblet cells, enteroendocrine cells, and Paneth cells. Tight-junction integrity and cytochrome P450 3A4 activity rise to physiological levels, and the mucus layer thickens to provide habitat for commensal microbiota. To accommodate strict anaerobes, Jalili-Firoozinezhad and colleagues developed an anaerobic intestine-on-a-chip in which the apical lumen is purged with nitrogen while the basolateral compartment receives oxygenated medium, generating a stable transmucosal oxygen gradient that supports a complex microbiome including Faecalibacterium prausnitzii for more than five days [30]. Gut chips have been used to study inflammatory bowel disease, host–microbiome cross-talk, oral drug absorption (including the species-divergent bioavailability of nifedipine and verapamil), and radiation-induced enteropathy.

5.6. Blood–brain barrier and brain-on-a-chip

The blood–brain barrier (BBB), formed by tightly junctioned brain microvascular endothelial cells in concert with pericytes and astrocytic end-feet, is one of the most formidable barriers to drug delivery and a major contributor to the failure of central nervous system drug development. The BBB-on-a-chip developed by Park and colleagues uses a two-channel design in which iPSC-derived brain microvascular endothelial cells line the upper channel, while astrocytes and pericytes embedded in a basement-membrane hydrogel occupy the lower channel [31]. Critically, the chip is operated under controlled hypoxia (5% O_2), which mimics the in vivo brain microenvironment and induces near-physiological

transendothelial electrical resistance (>2,500 Ω cm^2) and tight expression of the efflux transporters P-glycoprotein and breast cancer resistance protein [31]. More elaborate brain-on-a-chip designs add downstream compartments containing iPSC-derived neurons, astrocytes, and microglia—organized as cortical, hippocampal, or midbrain modules—and measure neuronal activity using integrated microelectrode arrays. Such platforms have been used to study amyloid-β–induced neurotoxicity in Alzheimer's disease, α-synuclein pathology in Parkinson's disease, neuroinflammation, and to predict CNS penetration of antibody therapeutics and antisense oligonucleotides [32].

5.7. Skin-on-a-chip and tumour-on-a-chip

Skin-on-a-chip systems reproduce the stratified architecture of human skin—keratinocyte-derived epidermis above a fibroblast-populated dermal compartment—on a perfused microfluidic platform; integration of melanocytes, dendritic cells, and endothelialized vascular channels enables modelling of UV damage, atopic dermatitis, psoriasis, and topical formulation permeation, and skin chips have gained importance following the European Union ban on animal testing for cosmetic ingredients [33]. Tumour-on-a-chip platforms reconstruct the tumour microenvironment—including hypoxic gradients, abnormal vasculature, immune infiltrate, stromal fibroblasts, and extracellular matrix stiffness—to enable physiologically relevant cancer drug screening. Patient-derived tumour organoids embedded in vascularized microfluidic chambers preserve histological architecture and mutational signatures and have been used to predict individual patient responses to chemotherapy, to study immune checkpoint blockade, CAR-T cell penetration, and metastatic dissemination [34].

Table 2 Major organ-on-a-chip models: cellular composition, key biomechanical cues, and representative applications.

Organ chip	Principal cell types	Key biomechanical / biochemical cue	Representative applications
Lung	Alveolar epithelium; pulmonary microvascular endothelium	Cyclic strain (~10%, 0.2 Hz); air–liquid interface	Pulmonary oedema; COPD; asthma; SARS-CoV-2 antivirals
Liver	Primary hepatocytes; LSECs; Kupffer & stellate cells	Continuous perfusion; oxygen zonation	DILI screening; CYP metabolism; NASH
Heart	iPSC-derived cardiomyocytes; cardiac fibroblasts	Electrical pacing; cantilever loading	QT prolongation; cardiotoxicity; cardiomyopathies
Kidney	PTECs; podocytes; renal microvascular endothelium	Luminal shear (~0.2 dyne/cm^2)	Nephrotoxicity; drug transport; ADPKD
Gut	Caco-2 / primary epithelium; microbiota	Peristaltic strain; transmucosal O_2 gradient	IBD; microbiome; oral bioavailability
BBB / Brain	iPSC-derived BMECs; astrocytes; pericytes	Hypoxia (5% O_2); shear	CNS drug penetration; neurodegeneration
Skin	Keratinocytes; fibroblasts; melanocytes	Air–liquid interface; perfusion	Cosmetics; dermatitis; transdermal drugs
Tumour	Patient-derived tumour cells; CAFs; immune cells	Hypoxia gradients; perfusable vasculature	Personalized chemo; immunotherapy screening

6. Multi-Organ and Body-on-a-Chip Platforms

Whole-body physiology depends on the integrated action of multiple organs connected through systemic circulation. Multi-organ-on-a-chip (MOoC) or body-on-a-chip platforms address this need by fluidically coupling two or more organ modules through shared microvascular circuits, enabling simulation of absorption, distribution, metabolism, and excretion (ADME) and inter-organ pharmacological cross-talk. Notable architectures include the TissUse HUMIMIC Chip2 and Chip3 platforms with integrated on-chip micropumps; the four-organ chip of Maschmeyer and colleagues that maintains co-culture of intestine, liver, kidney, and skin equivalents for up to 28 days [35]; and the ten-organ interrogator platform reported by Herland and colleagues, which fluidically couples gut, liver, and kidney chips to predict the oral bioavailability and renal clearance of nicotine and cisplatin in quantitative agreement with clinical pharmacokinetic data [36]. Ronaldson-Bouchard et al. subsequently demonstrated a four-organ chip connecting matured heart, liver, bone, and skin tissues for chronic drug exposure studies over four weeks [37]. These platforms

enable mechanistic pharmacokinetic–pharmacodynamic modelling, prediction of drug–drug interactions, and detection of secondary toxicities such as metabolite-mediated cardiotoxicity that are invisible in single-organ assays.

7. Pharmaceutical Applications

OoC platforms have entered routine use across the pharmaceutical value chain. In drug discovery, high-throughput-compatible plate formats such as the MIMETAS OrganoPlate® accommodate up to 96 independent organ models per plate, permitting parallel dose–response and combination studies on robotic liquid handlers; by placing physiology earlier in the discovery cascade, OoC platforms shift attrition from costly late-stage clinical failure toward inexpensive preclinical de-risking. For safety assessment, OoC platforms outperform conventional models for the four toxicities responsible for the majority of attrition—hepatotoxicity, cardiotoxicity, nephrotoxicity, and neurotoxicity—and the validated quantitative performance of the Emulate Liver-Chip (87% sensitivity, 100% specificity) [14] together with multi-laboratory reproducibility studies of MIMETAS and CN Bio kidney chips have established OoC platforms as credible alternatives to two-species animal toxicology for selected endpoints.

OoC platforms have also been used to recapitulate diseases poorly served by animal models—including chronic obstructive pulmonary disease, cystic fibrosis, inflammatory bowel disease, non-alcoholic steatohepatitis, polycystic kidney disease, Alzheimer's and Parkinson's diseases—and an expanding range of inherited disorders through patient-derived iPSC-on-chip platforms. Perhaps most transformative is precision medicine: tumour biopsies cultured as patient-derived organoids on chip have been shown to predict individual chemotherapy response in colorectal, pancreatic, and breast cancer with concordance above 80% [38], cystic fibrosis intestinal organoid-on-chip assays now identify patients who will respond to specific CFTR modulator combinations, and iPSC-derived cardiac chips are entering clinical use for predicting individual susceptibility to chemotherapy-induced cardiotoxicity. The COVID-19 pandemic further demonstrated the strategic value of OoC platforms in pandemic preparedness: within weeks of the emergence of SARS-CoV-2, alveolus, airway and gut chips were used to model viral entry and screen approved drugs, contributing to the prioritization of amodiaquine and the de-prioritization of hydroxychloroquine [22].

8. Commercial Landscape and Regulatory Perspectives

The commercial OoC landscape has matured rapidly since 2018. Emulate Inc. (Boston, MA, USA), spun out of the Wyss Institute, supplies the Human Emulation System with validated Liver-, Lung-, Brain-, Kidney-, and Intestine-Chips and was the first company whose data were accepted by the FDA in support of an IND submission [14]. MIMETAS B.V. (Leiden, Netherlands) markets the OrganoPlate® 96-well microfluidic platform compatible with standard laboratory automation; TissUse GmbH (Berlin, Germany) offers the HUMIMIC multi-organ systems; CN Bio Innovations (Cambridge, UK) markets PhysioMimix™ liver and gut platforms; Hesperos Inc. (Orlando, FL, USA) commercializes the Human-on-a-Chip® body-on-chip system with pumpless gravity-driven flow; and AlveoliX (Switzerland), Nortis (USA), and a growing number of regional vendors serve specialized niches. Combined, these companies have driven the global OoC market from less than USD 50 million in 2020 to a projected USD 600 million by 2028 [39].

Table 3 Selected commercial organ-on-a-chip platforms (2024–2025).

Company (country)	Product line	Format / capacity	Key applications / milestones
Emulate, Inc. (USA)	Human Emulation System; Liver/Lung/Brain/Intestine/Kidney-Chip	Single-chip cartridge with Zoë culture module	FDA-accepted Liver-Chip data in IND submission (2022)
MIMETAS B.V. (Netherlands)	OrganoPlate® 3-lane / 2-lane / Graft	96-well microfluidic plate; up to 96 chips/plate	High-throughput screening; vascularized tumour models
TissUse GmbH (Germany)	HUMIMIC Chip2 / Chip3 / Chip-X	2–3 organ modules; on-chip peristaltic pump	Multi-organ ADME; chronic exposure ≥28 days

CN Bio Innovations (UK)	PhysioMimix™ Single-/Multi-organ	Plate-based, automated perfusion	Liver DILI; gut–liver axis; NASH
Hesperos, Inc. (USA)	Human-on-a-Chip®	Up to 5-organ pumpless gravity-driven	PK/PD modelling; neuromuscular disorders
AlveoliX (Switzerland)	AXLung-on-Chip	Breathing lung array	Respiratory toxicology

Regulatory acceptance has accelerated decisively in the past three years. The United States FDA Modernization Act 2.0, signed into law on 29 December 2022, removed the longstanding statutory requirement that new drugs be tested in two animal species, and explicitly named cell-based assays, organ chips, microphysiological systems, and computer modelling among acceptable alternatives [6]. The FDA Predictive Toxicology Roadmap and the Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program provide formal regulatory pathways for OoC qualification. Internationally, the European Medicines Agency and Health Canada have endorsed New Approach Methodologies (NAMs), and the IQ Microphysiological Systems Affiliate—a pre-competitive consortium of more than thirty pharmaceutical companies—has established multi-laboratory reproducibility benchmarks accelerating regulatory qualification. In May 2025, the FDA announced a phased roadmap to reduce, refine, and ultimately replace animal testing for monoclonal antibodies and other biologics, citing OoC, AI-based, and human-relevant in vitro approaches as central pillars [40].

9. Challenges and Limitations

Despite striking progress, several technical and translational challenges remain. Standardization of device geometry, cell sources, perfusion protocols, and readouts across laboratories is a prerequisite for routine regulatory qualification; this is being addressed by the IQ-MPS Affiliate and the European ORCHID consortium through inter-laboratory ring trials. PDMS-mediated absorption of hydrophobic small molecules continues to confound pharmacokinetic measurements in early-generation chips and is driving migration toward thermoplastic and glass devices [14]. Reconstitution of a competent functional vasculature within organ chips remains technically demanding, although recent advances in self-assembled perfusable microvasculature and sacrificial templating are narrowing the gap [19], and integration of innate and adaptive immunity—particularly the recruitment of circulating immune cells and the formation of lymphoid microenvironments—remains an active area of development. Scalability, cost per data point, and clear context-of-use definitions for each platform must continue to improve if OoC is to displace conventional preclinical platforms across the discovery pipeline.

10. Future Perspectives

Four convergent trends are likely to reshape OoC technology over the next decade. Integration with artificial intelligence and machine learning—both for analysis of multi-modal sensor streams and for model-based extrapolation of chip data to whole-body pharmacokinetics—will transform OoC platforms into closed-loop autonomous experimentation systems. Combination with single-cell and spatial omics technologies will yield unprecedented mechanistic resolution of drug effects within chip tissues. Convergence with patient-derived iPSCs and CRISPR-edited isogenic controls will enable truly personalized precision-medicine platforms for routine clinical decision support. Finally, body-on-a-chip platforms integrating six or more organs with physiologically scaled fluid volumes are expected to enter regulatory submissions for first-in-human dose selection within five years, potentially redefining the boundary between preclinical and clinical drug development [41,42].

11. Conclusion

Organ-on-a-chip technology has progressed in slightly more than a decade from a single proof-of-concept demonstration of a breathing lung in a microchip to a regulated, commercially mature platform underpinning pharmaceutical decision-making at major drug developers and accepted by the United States Food and Drug Administration in support of investigational new drug applications. By recreating the architecture, mechanical environment, perfusion, and tissue–tissue interfaces of native human organs—the cyclic stretching of the lung alveolus, the perfused hepatic sinusoid, the shear-driven kidney proximal tubule, the peristaltic and microbe-bearing gut, the hypoxia-induced blood–brain barrier, and the iPSC-driven maturing heart—OoC systems address the predictive

limitations of two-dimensional culture and animal models that have constrained drug development for a century. Integration with induced pluripotent stem cells, vascularized multi-organ circuits, artificial intelligence, omics readouts, and personalized patient samples positions the field at the centre of next-generation precision pharmaceutical research. With the recent removal of statutory animal testing requirements through the FDA Modernization Act 2.0 and the rapid growth of the New Approach Methodologies framework, organ-on-a-chip technology stands poised not merely to complement but in many domains to replace conventional preclinical models, accelerating the delivery of safer, more effective, and more personalized therapies to patients worldwide.

Compliance with Ethical Standards

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Disclosure of Conflict of Interest

The authors declare no financial or non-financial conflicts of interest related to the subject matter of this manuscript.

Statement of Ethical Approval

This review article is based exclusively on previously published literature and does not involve any new studies on human participants or animals performed by the authors. Ethical approval and informed consent are therefore not applicable.

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