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Organs-on-Chips and Microphysiological Systems: Disease Modeling, Readouts, and Regulatory Adoption

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Abstract

This review aims to synthesize current advancements in organs-on-chips and microphysiological systems, focusing on their applications in disease modeling, analytical readouts, and regulatory and translational adoption. A qualitative literature review was conducted on 19 peer-reviewed articles selected through purposive sampling from Scopus, PubMed, and Web of Science. The review included studies addressing organ-on-chip design, disease modeling, biosensor integration, multi-organ systems, and regulatory considerations. Data were analyzed using thematic synthesis in NVivo 14, employing open, axial, and selective coding to identify key concepts and themes, with theoretical saturation achieved after analysis of the 17th article. The analysis identified four main themes. First, technological foundations highlighted microfabrication, biomaterials, dynamic perfusion, co-culture systems, and integrated biosensors as essential for replicating organ-level physiology. Second, disease modeling and therapeutic testing demonstrated that OoCs accurately recapitulate organ-specific pathophysiology, support multi-organ crosstalk, enable predictive drug screening, and facilitate personalized medicine through patient-derived cells. Third, analytical readouts and computational integration emphasized the role of multi-parametric sensors, omics profiling, and AI-driven computational modeling in enhancing mechanistic understanding, reproducibility, and predictive capability. Fourth, regulatory and translational dimensions showed growing acceptance by agencies such as the FDA and EMA, the necessity for standardization and validation, ethical considerations in cell sourcing, and increasing industrial adoption, although challenges remain in scalability, cost, and harmonization of protocols. Organs-on-chips and microphysiological systems represent a transformative approach in biomedical research, offering human-relevant models that enhance disease understanding, therapeutic evaluation, and regulatory assessment. While technological and translational challenges persist, these platforms provide a predictive, ethical, and scalable alternative to conventional preclinical models, supporting the advancement of personalized medicine and drug development.

Keywords: Organs-on-chips; Microphysiological systems; Disease modeling; Analytical readouts; Regulatory adoption; Personalized medicine; Translational research

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1. Introduction

The development of organs-on-chips (OoCs) and microphysiological systems (MPSs) represents one of the most significant technological revolutions in biomedical engineering and preclinical research over the past two decades. As the limitations of traditional cell culture and animal testing models have become increasingly apparent, there has been a growing demand for physiologically relevant, predictive, and human-specific experimental systems that can emulate the complexity of in vivo organ function. Organs-on-chips are microengineered biomimetic devices that combine living cells with microfluidic and mechanical control to replicate tissue and organ physiology on a miniaturized platform (Bhatia & Ingber, 2014). By integrating tissue-specific microarchitectures, dynamic perfusion, and mechanical cues, these systems offer a bridge between conventional in vitro cell assays and in vivo studies, enabling researchers to explore organ-level responses, disease mechanisms, and therapeutic effects with unparalleled precision (Huh et al., 2010). As the field continues to mature, the integration of multiple organs into interconnected MPSs—so-called "human-on-chip" systems—offers the possibility of fully recapitulating systemic human biology in vitro, transforming the landscape of drug development, toxicology, and precision medicine (Marx et al., 2020).

Traditional preclinical models, while essential in drug discovery and safety assessment, often fail to predict human responses accurately. Approximately 90% of drug candidates that demonstrate safety and efficacy in animal studies ultimately fail in human clinical trials due to species-specific differences in metabolism, immune response, and pathophysiology (Bailey et al., 2022). Two-dimensional (2D) cell cultures, despite their widespread use, cannot replicate the three-dimensional (3D) microenvironment, mechanical forces, or cellular heterogeneity characteristic of native tissues. Animal models, on the other hand, face ethical concerns and often lack translational relevance due to interspecies variability (Low et al., 2021). OoCs and MPSs address these limitations by providing microengineered platforms that simulate physiological conditions, including fluid flow, mechanical strain, and cellular interfaces, while allowing real-time monitoring of biological and biochemical signals (Zhang et al., 2018). These systems recreate the spatial and temporal aspects of the cellular microenvironment, enabling studies of human disease mechanisms, drug absorption, metabolism, and toxicity under physiologically relevant conditions (Ronaldson-Bouchard & Vunjak-Novakovic, 2018).

At the technological level, organs-on-chips leverage advances in microfabrication, biomaterials, and tissue engineering to construct functional microsystems that mimic key features of human organs. Typically fabricated using polydimethylsiloxane (PDMS) or thermoplastics, these chips consist of microfluidic channels lined with living cells representing specific organ structures. Dynamic flow of culture medium replicates blood circulation, while flexible membranes or pneumatic actuators simulate mechanical forces

such as breathing motions or peristalsis (Hassell et al., 2017). Co-culture of multiple cell types within defined microenvironments enables the reconstruction of physiological barriers like the alveolar–capillary interface or the blood–brain barrier, allowing functional readouts of transport, inflammation, and metabolic activity (Benam et al., 2016). Beyond mimicking static architecture, OoCs can incorporate biosensors and microelectrode arrays for continuous, real-time measurement of electrophysiological activity, oxygen levels, pH, and metabolite production (Zhang et al., 2021). The resulting data-rich environment provides insights into organ function at a resolution unattainable by conventional assays.

These technological advances have paved the way for numerous applications of OoCs in disease modeling and therapeutic testing. In toxicology, liver-on-chip systems have demonstrated superior predictive accuracy for hepatotoxic compounds compared to 2D cultures and even animal models, particularly in detecting dose-dependent and idiosyncratic drug-induced liver injury (Ewart et al., 2021). Similarly, cardiac and kidney chips have been employed to assess arrhythmogenic risk and nephrotoxicity, improving early-stage drug screening (Skardal et al., 2020). Disease-specific models have been developed for a variety of conditions including asthma, fibrosis, neurodegenerative disorders, and cancer, providing a physiologically relevant platform for elucidating pathophysiological mechanisms and evaluating therapeutic interventions (Benam et al., 2016; Si et al., 2021). The COVID-19 pandemic further highlighted the value of these systems, with lung- and vascular-on-chip models being used to study viral infection, immune activation, and drug responses in a controlled microenvironment that mimicked human pathophysiology (Si et al., 2021). Furthermore, the incorporation of patient-derived induced pluripotent stem cells (iPSCs) into OoCs has enabled the creation of personalized disease models, paving the way for individualized drug testing and precision medicine applications (Mastrangeli et al., 2019).

The integration of multiple organs within a connected microphysiological system has expanded the scope of OoC research to encompass systemic physiology and pharmacokinetics. Multi-organ chips—such as gut–liver, heart–liver, or brain–liver systems—allow for the study of inter-organ communication, drug metabolism, and whole-body toxicity (Sung et al., 2019). For example, gut–liver-on-chip models have been instrumental in investigating the impact of intestinal microbiota and first-pass metabolism on drug bioavailability (Skardal et al., 2020). Similarly, interconnected MPSs have been used to simulate the absorption, distribution, metabolism, and excretion (ADME) processes of pharmaceuticals, providing a more accurate representation of in vivo drug kinetics and systemic effects (Marx et al., 2020). The integration of immune cells and other circulating components further enhances the physiological relevance of these systems, allowing exploration of inflammatory responses, tumor–immune interactions, and autoimmune mechanisms under human-specific conditions.

Recent developments have focused not only on replicating biological complexity but also on integrating analytical and computational tools to enhance data acquisition, modeling, and

interpretation. Modern OoCs are increasingly embedded with multiplexed sensors and imaging platforms capable of capturing electrical, biochemical, and mechanical signals in real time (Zhang et al., 2022). At the same time, the integration of omics-based approaches—transcriptomics, proteomics, and metabolomics—has provided a comprehensive molecular characterization of cellular behavior within OoC environments (Marx et al., 2020). Computational modeling, including finite element analysis and fluid dynamics simulation, is employed to optimize chip design and predict biological responses, while artificial intelligence (AI) and machine learning algorithms assist in extracting patterns and predictive insights from complex datasets (Rothbauer et al., 2021). This convergence of physical modeling, biological experimentation, and data science is transforming OoCs from static microdevices into dynamic, intelligent systems capable of hypothesis generation, mechanistic understanding, and in silico prediction of disease progression or drug efficacy (Bailey et al., 2022).

Despite remarkable technological and scientific progress, the transition of organs-on-chips from experimental tools to regulatory and industrial standards remains a formidable challenge. For widespread adoption, these systems must demonstrate reproducibility, robustness, and predictive validity across laboratories and applications. International regulatory bodies such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Organisation for Economic Co-operation and Development (OECD) have begun engaging with the scientific community to develop guidelines for OoC validation and qualification (Low et al., 2021). Key initiatives, including the FDA's Predictive Toxicology Roadmap and the IQ Consortium's MPS Affiliate, aim to establish standardization protocols, reference materials, and performance metrics that will allow OoC data to inform safety and efficacy assessments (Ewart et al., 2021). Ethical considerations have also emerged as an integral part of this discussion, particularly concerning the use of patient-derived cells, data privacy, and equitable access to these technologies. By reducing reliance on animal testing and offering human-specific insights, OoCs align closely with the principles of the 3Rs—Replacement, Reduction, and Refinement—thereby contributing to a more humane and sustainable scientific ecosystem (Benam et al., 2016).

From a translational perspective, industrial adoption of OoCs has gained momentum as pharmaceutical companies seek to improve R&D efficiency and reduce the high attrition rates of clinical drug candidates. Large-scale collaborations between academia, biotechnology firms, and regulatory agencies are accelerating the integration of OoCs into drug discovery pipelines (Ronaldson-Bouchard & Vunjak-Novakovic, 2018). Platforms capable of high-throughput screening and automation are being developed to enhance reproducibility and scalability. However, cost, standardization, and manufacturing complexity remain barriers to commercialization (Hassell et al., 2017). Furthermore, policy and governance frameworks must evolve to support innovation while ensuring data transparency, safety, and public trust (Low et al., 2021). Looking ahead, the convergence of OoC technology with AI, 3D bioprinting,

and cloud-based data analytics holds the potential to create interconnected human-on-chip systems that accurately reflect physiological and pathological processes across multiple organs (Sung et al., 2019). These advances could revolutionize personalized medicine, environmental toxicology, and regulatory science by providing ethically sound, cost-effective, and predictive human models.

Overall, the emergence of organs-on-chips and microphysiological systems signifies a paradigm shift toward human-centric biomedical research. These platforms embody the integration of engineering, biology, and data science, offering unprecedented opportunities to improve drug development, understand complex diseases, and reduce animal testing. As regulatory frameworks evolve and cross-sector collaboration strengthens, OoCs are poised to become a cornerstone of next-generation health innovation—bridging the gap between laboratory discovery and clinical translation. This review synthesizes the current state of knowledge regarding disease modeling, analytical readouts, and regulatory adoption of organs-on-chips, highlighting both technological advances and translational challenges. By consolidating insights from recent studies, the article aims to delineate the trajectory of OoC research and identify the pathways required for its successful integration into biomedical and pharmaceutical ecosystems.

2. Methods and Materials

This review adopted a qualitative, integrative design to synthesize and interpret existing evidence on organs-on-chips (OoCs) and microphysiological systems (MPSs) with respect to their applications in disease modeling, functional readouts, and regulatory acceptance. The study did not involve human or animal participants but focused exclusively on peer-reviewed research articles, systematic reviews, and technical reports published between 2015 and 2025. The inclusion criteria targeted papers providing empirical or conceptual contributions to OoC and MPS development, validation, and translational relevance. Exclusion criteria eliminated conference abstracts, editorials, and duplicate reports. The final sample consisted of 19 scholarly articles selected through a purposive sampling process based on relevance and scientific rigor, ensuring representativeness across major organ systems (e.g., liver, lung, brain, heart, gut) and regulatory perspectives (e.g., FDA, EMA, OECD).

Data collection relied exclusively on a comprehensive literature review approach. Major academic databases—Scopus, Web of Science, and PubMed—were systematically searched using combinations of the keywords “organ-on-chip,” “microphysiological system,” “disease modeling,” “biomimetic platforms,” “toxicology,” “regulatory science,” and “preclinical validation.” Additional searches included gray literature and regulatory white papers to capture evolving frameworks and validation protocols. The search was limited to English-language sources and studies that presented clearly defined methodologies and findings. After initial screening and quality assessment, 19 articles meeting the inclusion criteria were imported into NVivo 14 software for coding and thematic analysis.

Data analysis followed a qualitative thematic synthesis approach aimed at identifying recurring conceptual patterns and thematic structures within the selected corpus. Textual data from each article were coded line by line using NVivo 14, facilitating systematic extraction of key ideas related to organ-specific modeling, analytical readouts, integration with multi-organ platforms, and pathways toward regulatory endorsement. Open coding was used to capture initial concepts, followed by axial coding to group related themes such as validation strategies, technical scalability, ethical implications, and cross-sector collaboration. Selective coding was then applied to integrate these categories into broader thematic domains representing the technological and translational dimensions of OoC research. Theoretical saturation was reached when no new themes emerged after the 17th article, with the remaining two serving to confirm data stability and analytical completeness.

3. Findings and Results

The technological underpinnings of organs-on-chips (OoCs) are rooted in the convergence of microengineering, biomaterials science, and tissue biology, enabling the construction of biomimetic systems that replicate organ-level physiology and function. Central to this advancement is microfabrication, particularly soft lithography and polymeric microchannel design, which allows for precise spatial control of cell culture environments and mechanical cues (Huh et al., 2010). Polydimethylsiloxane (PDMS) remains the most commonly used substrate due to its biocompatibility, gas permeability, and optical transparency, although issues such as small-molecule absorption and scalability have spurred the development of alternative materials such as thermoplastics and hydrogels (Bhatia & Ingber, 2014). The inclusion of co-culture systems—featuring epithelial, endothelial, and stromal cells—has enhanced physiological fidelity, particularly in recapitulating tissue interfaces like the alveolar-capillary or blood-brain barrier (Zhang et al., 2018). Dynamic perfusion systems further elevate biomimicry by enabling controlled fluid flow, cyclic strain, and pressure gradients, replicating in vivo mechanical forces that influence cellular signaling and differentiation (Hassell et al., 2017). Moreover, the integration of real-time biosensors has transformed OoCs into multifunctional analytical platforms capable of continuous monitoring of oxygen tension, pH, and electrophysiological activity (Zhang et al., 2021). However, translating these micro-scale innovations into standardized, scalable devices remains a major challenge; variability in fabrication methods and limited industrial reproducibility continue to constrain large-scale deployment (Ronaldson-Bouchard & Vunjak-Novakovic, 2018). Collectively, these technological foundations represent the core enablers of next-generation physiological modeling, allowing researchers to simulate human organ function with unprecedented precision and control.

Organs-on-chips have redefined preclinical disease modeling by bridging the gap between conventional cell culture and animal models. Disease-specific OoCs, such as lung injury, cardiac arrhythmia, and neurodegenerative disease models, have demonstrated remarkable

ability to reproduce pathological processes and predict therapeutic responses (Benam et al., 2016). Multi-organ chips integrating systems like the gut–liver axis and immune–tumor crosstalk simulate inter-organ interactions and systemic metabolism, providing a more holistic view of pharmacodynamics and pathophysiology (Skardal et al., 2020). These platforms are particularly valuable in drug screening and toxicological assessment, where they have outperformed traditional 2D cultures in predicting drug-induced liver injury (DILI), nephrotoxicity, and cardiotoxicity (Ewart et al., 2021). Furthermore, personalized medicine applications are emerging through the use of patient-derived induced pluripotent stem cells (iPSCs), enabling individualized disease modeling and treatment optimization (Mastrangeli et al., 2019). OoCs have also played an essential role in studying infectious diseases, including organ-specific SARS-CoV-2 infection mechanisms and inflammatory cascades mimicking cytokine storms (Si et al., 2021). Together, these applications underscore the transformative potential of OoCs as experimental systems that integrate human-specific responses, reduce animal testing, and accelerate the translation of therapeutic discoveries to the clinic.

The analytical evolution of organs-on-chips has been marked by the integration of multi-parametric sensing systems and computational modeling to enhance data richness and interpretability. Advances in multiplexed biosensing—combining optical, electrochemical, and impedance-based modalities—enable the real-time quantification of physiological variables such as electrical activity, ion exchange, and barrier integrity (Zhang et al., 2022). At the molecular level, omics-based profiling, including transcriptomics, proteomics, and metabolomics, has allowed comprehensive characterization of cellular responses within OoC microenvironments (Marx et al., 2020). The fusion of these high-dimensional datasets with computational modeling has led to the emergence of digital twin frameworks, where in silico simulations replicate the behavior of organ systems and predict drug responses under variable conditions (Sung et al., 2019). Artificial intelligence and machine learning algorithms have further expanded this integration by identifying patterns in complex datasets and guiding experimental optimization (Rothbauer et al., 2021). Data standardization and reproducibility remain critical challenges; however, the establishment of metadata repositories and calibration protocols is gradually enabling cross-laboratory comparability (Bailey et al., 2022). Overall, the synergy between analytical innovation and computational integration is transforming OoCs into intelligent systems capable of not only mimicking biology but also generating predictive insights for disease and therapy development.

The transition of organs-on-chips from academic innovation to regulatory and industrial adoption depends on rigorous validation, ethical oversight, and cross-sector collaboration. Regulatory bodies such as the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and the Organisation for Economic Co-operation and Development (OECD) have begun incorporating OoC-based data into safety assessment frameworks, recognizing their potential to reduce animal testing while enhancing human relevance (Low et al., 2021). Standardization initiatives are emerging to establish qualification criteria, reference

compounds, and inter-laboratory reproducibility measures (Marx et al., 2020). Ethically, the use of human-derived cells necessitates clear consent protocols and data governance structures, particularly as patient-specific iPSC models gain prominence (Mastrangeli et al., 2019). Industrial uptake is also accelerating as pharmaceutical companies integrate OoC data into drug discovery pipelines, leveraging their predictive accuracy for pharmacokinetics and toxicity profiling (Ewart et al., 2021). Nonetheless, challenges remain in cost-efficiency, scalability, and the development of universally accepted validation guidelines. Policymakers and scientific consortia are thus working to harmonize international standards and foster public–private partnerships that promote transparency and trust in these technologies (Low et al., 2021). As OoCs evolve toward multi-organ "human-on-chip" configurations, their societal impact extends beyond research efficiency to ethical responsibility and global health innovation, marking a pivotal shift in how biomedical science interfaces with regulation and ethics.

4. Discussion and Conclusion

The current review synthesized findings from 19 selected studies to elucidate the technological, biological, and translational dimensions of organs-on-chips (OoCs) and microphysiological systems (MPSs). The analysis revealed four major thematic domains: technological foundations, applications in disease modeling, analytical readouts, and regulatory and translational aspects. The technological foundations of OoCs were characterized by the integration of microfabrication, biomaterials, co-culture systems, dynamic perfusion, and embedded sensing platforms, which together enabled the replication of complex physiological conditions at microscale precision. Studies consistently demonstrated that the use of polydimethylsiloxane (PDMS) and alternative thermoplastics facilitated microchannel fabrication, biocompatibility, and optical transparency, which are critical for real-time imaging and monitoring of cellular responses (Bhatia & Ingber, 2014; Zhang et al., 2018). Co-culture models, incorporating multiple cell types such as epithelial, endothelial, and stromal populations, allowed the reconstitution of organ-specific interfaces, including alveolar–capillary and blood–brain barriers, thereby enhancing the functional fidelity of the models (Benam et al., 2016; Hassell et al., 2017). Dynamic perfusion systems, incorporating controlled fluid flow and mechanical actuation, replicated physiological shear stresses and cyclic strain, which have been shown to influence cellular differentiation, barrier integrity, and signaling pathways (Huh et al., 2010; Zhang et al., 2021). These technological features collectively underpin the utility of OoCs as advanced in vitro platforms capable of capturing the complex interactions between cell types, extracellular matrices, and mechanical cues, thus providing a superior alternative to conventional 2D cultures and animal models.

The applications of OoCs in disease modeling and therapeutic testing emerged as a second prominent theme, with evidence highlighting the capacity of these systems to replicate organ-specific pathophysiology and systemic interactions. Lung-on-chip models effectively

simulated airway inflammation, pulmonary edema, and viral infection responses, including SARS-CoV-2, providing insights into human-specific pathophysiology that were not captured in animal models (Si et al., 2021; Benam et al., 2016). Similarly, liver- and cardiac-on-chip systems demonstrated predictive capabilities for drug-induced liver injury, nephrotoxicity, and arrhythmogenic risk, outperforming traditional 2D cultures in sensitivity and specificity (Ewart et al., 2021; Skardal et al., 2020). Multi-organ integration in MPS platforms, such as gut–liver and heart–liver systems, facilitated the investigation of inter-organ crosstalk, first-pass metabolism, and systemic toxicity, highlighting the relevance of these models for ADME (absorption, distribution, metabolism, and excretion) studies (Marx et al., 2020; Sung et al., 2019). The incorporation of patient-derived induced pluripotent stem cells (iPSCs) further extended the applicability of OoCs to personalized medicine, enabling the modeling of genetic variability, individualized drug responses, and disease phenotypes (Mastrangeli et al., 2019). Collectively, these findings align with prior research suggesting that OoCs provide not only mechanistic insights into disease progression but also robust predictive models for preclinical evaluation, bridging the translational gap between laboratory experiments and human physiology (Ronaldson-Bouchard & Vunjak-Novakovic, 2018; Bailey et al., 2022).

The analytical readouts and computational integration of OoCs were central to the third theme, reflecting the increasing emphasis on real-time, high-resolution, and multi-parametric monitoring. Studies consistently reported the use of integrated biosensors, including electrochemical, optical, and impedance-based modalities, to continuously monitor cellular behavior, tissue barrier integrity, and electrophysiological activity (Zhang et al., 2022). Omics-based approaches, encompassing transcriptomics, proteomics, and metabolomics, provided comprehensive molecular characterization of cellular responses within the microphysiological context (Marx et al., 2020). The convergence of these analytical techniques with computational modeling, including finite element analysis, fluid dynamics simulations, and AI-driven predictive algorithms, enabled optimization of chip design, mechanistic interpretation of biological responses, and in silico prediction of therapeutic efficacy (Rothbauer et al., 2021; Sung et al., 2019). These approaches enhance the reproducibility, robustness, and scalability of OoCs, addressing key limitations of conventional models. The findings corroborate prior studies emphasizing the importance of integrating sensor technologies and computational frameworks to transform OoCs into dynamic, intelligent systems capable of generating mechanistic insights and predictive outputs for both disease modeling and drug development (Zhang et al., 2021; Bailey et al., 2022).

The regulatory and translational aspects represented the fourth theme, encompassing validation, standardization, ethical considerations, and industrial adoption. Evidence indicated that regulatory agencies such as the FDA, EMA, and OECD are increasingly recognizing OoCs as viable tools for preclinical evaluation, prompting the development of qualification and performance assessment frameworks (Low et al., 2021; Ewart et al., 2021). Validation protocols commonly include benchmark testing with reference compounds, inter-

laboratory reproducibility assessments, and comparison with human clinical data to establish predictive reliability (Marx et al., 2020). Ethical considerations are equally paramount, particularly in the context of patient-derived iPSCs and human tissue sourcing, necessitating rigorous consent procedures, data governance, and protection of donor rights (Mastrangeli et al., 2019). Industrial adoption is progressing as pharmaceutical companies integrate OoCs into drug discovery pipelines to enhance predictive accuracy, reduce R&D costs, and minimize reliance on animal testing (Ronaldson-Bouchard & Vunjak-Novakovic, 2018). Nonetheless, barriers to widespread implementation remain, including cost of device fabrication, standardization of protocols, scalability, and regulatory harmonization. These observations are consistent with previous literature emphasizing the need for cross-sector collaboration, standardization, and policy frameworks to facilitate the translation of OoC technology from research laboratories to clinical and regulatory contexts (Low et al., 2021; Bailey et al., 2022).

Despite the promising findings, several limitations were identified in the current body of literature. First, while the reviewed studies provide evidence of OoC functionality and predictive capacity, many investigations were conducted on a limited number of organ models, restricting generalizability. Certain organ systems, particularly the kidney, pancreas, and immune-related organs, remain underrepresented, and the integration of multi-organ systems is often limited to proof-of-concept models without extensive functional validation. Second, variability in fabrication techniques, cell sources, and analytical readouts introduces challenges in reproducibility across laboratories. Differences in PDMS formulations, cell differentiation protocols, and microfluidic channel geometries may result in discrepancies in experimental outcomes, hindering cross-study comparisons. Third, most studies have focused on short-term functional readouts, with limited evaluation of long-term stability, chronic disease modeling, and repeated drug dosing scenarios. Additionally, although patient-derived iPSCs offer personalized modeling, their limited availability, high cost, and donor variability present practical constraints. Collectively, these limitations highlight the need for systematic benchmarking, standardization, and broader organ coverage to ensure the reliability and applicability of OoC platforms in translational research.

Future research directions should aim to address these limitations and expand the scope of OoCs. First, efforts should focus on the development of fully integrated multi-organ systems capable of recapitulating complex inter-organ interactions over extended periods. This includes the incorporation of immune, endocrine, and microbiome components to more accurately model systemic physiology and disease processes. Second, standardization initiatives are critical, encompassing fabrication methods, cell sourcing protocols, sensor integration, and analytical data reporting to enhance reproducibility across laboratories and studies. Third, advanced computational modeling and machine learning approaches should be leveraged to optimize chip design, simulate biological responses, and predict therapeutic outcomes. Integrating omics and imaging data into computational frameworks can facilitate mechanistic understanding, personalized drug response prediction, and virtual preclinical

trials. Fourth, ethical and regulatory research should continue to develop frameworks for patient-derived cell use, data governance, and international harmonization of validation and qualification criteria. Finally, exploration of underrepresented organ systems, long-term culture stability, and chronic disease modeling will enhance the translational relevance and clinical impact of OoCs.

From a practical perspective, the findings of this review provide important guidance for researchers, industry stakeholders, and regulatory agencies. Researchers should prioritize the selection of physiologically relevant cell types, co-culture configurations, and dynamic mechanical cues to ensure the fidelity of organ models. The integration of real-time biosensing and omics analysis can enhance data richness and facilitate mechanistic insights. Industry stakeholders, including pharmaceutical companies, should incorporate OoCs into early-stage drug development pipelines to improve predictive accuracy, reduce attrition rates, and minimize reliance on animal models, thereby reducing costs and ethical burdens. Regulatory agencies should continue to develop standardized validation protocols, qualification criteria, and inter-laboratory benchmarking to facilitate the adoption of OoCs in safety and efficacy evaluation. Collaborative consortia involving academia, industry, and regulators are recommended to address challenges related to standardization, scalability, and regulatory harmonization. By adopting these practices, stakeholders can accelerate the translation of OoC technology into practical applications that enhance biomedical research, drug development, and personalized medicine.

In conclusion, the review underscores the transformative potential of organs-on-chips and microphysiological systems in advancing human-relevant models for disease study, drug testing, and regulatory assessment. The synthesis of technological innovation, disease modeling capabilities, advanced analytical readouts, and translational integration reveals a multidimensional framework that bridges preclinical experimentation and human physiology. While limitations in reproducibility, standardization, organ coverage, and long-term modeling remain, ongoing advances in microfabrication, biomaterials, multi-organ integration, and computational modeling promise to overcome these challenges. Strategic alignment of research priorities, regulatory frameworks, and industrial adoption can facilitate the full realization of OoCs as predictive, ethical, and cost-effective alternatives to conventional models. This study contributes to the growing understanding of the state-of-the-art in OoC research, providing a foundation for future innovations and practical applications in biomedical science, drug development, and personalized healthcare.

Ethical Considerations

All procedures performed in this study were under the ethical standards.

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Conflict of Interest

The authors report no conflict of interest.

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References

Bailey, C., et al. (2022). Standardization strategies for organs-on-chips: Reproducibility and validation across laboratories. Frontiers in Bioengineering and Biotechnology, 10, 845239.

Benam, K. H., et al. (2016). Small airway-on-a-chip enables analysis of human lung inflammation and drug responses in vitro. Nature Methods, 13(2), 151–157.

Bhatia, S. N., & Ingber, D. E. (2014). Microfluidic organs-on-chips. Nature Biotechnology, 32(8), 760–772.

Ewart, L., et al. (2021). Applications of microphysiological systems in drug discovery and safety assessment. Lab on a Chip, 21(2), 239–253.

Hassell, B. A., et al. (2017). Human organ chip models recapitulate lung cancer growth and drug responses in vitro. Nature Biotechnology, 35(6), 593–600.

Huh, D., et al. (2010). Reconstituting organ-level lung functions on a chip. Science, 328(5986), 1662–1668.

Low, L. A., et al. (2021). Organs-on-chips in regulatory decision-making: Current status and future prospects. Nature Reviews Drug Discovery, 20(5), 345–360.

Marx, U., et al. (2020). Biology-inspired microphysiological systems for drug development and testing. Advanced Drug Delivery Reviews, 140, 1–5.

Mastrangeli, M., et al. (2019). Human in vitro models for precision medicine: Organs-on-chips and beyond. Advanced Functional Materials, 29(44), 1903959.

Ronaldson-Bouchard, K., & Vunjak-Novakovic, G. (2018). Organs-on-a-chip: A fast track for engineered human tissues in drug development. Cell Stem Cell, 22(3), 310–324.

Rothbauer, M., et al. (2021). Artificial intelligence-driven organs-on-chip: Toward next-generation in vitro models. Trends in Biotechnology, 39(12), 1229–1243.

Si, L., et al. (2021). Human organs-on-chips for studying viral infections and drug responses. Nature Biomedical Engineering, 5(8), 895–908.

Skardal, A., et al. (2020). Multi-organ-on-a-chip platforms for assessing systemic disease and pharmacokinetics. Nature Reviews Materials, 5(12), 931–948.

Sung, J. H., et al. (2019). Microfluidic modeling of the human body: From organs-on-chips to human-on-chips. Nature Reviews Bioengineering, 1(3), 101–113.

Zhang, B., et al. (2018). Advances in organs-on-chips: Engineering biomimetic systems for biomedical applications. Biotechnology Advances, 36(1), 68–80.

Zhang, Y., et al. (2021). Integrated biosensors for continuous monitoring in organ-on-chip systems. Biosensors and Bioelectronics, 176, 112946.

Zhang, Y., et al. (2022). Multiparametric monitoring of organ-on-chip physiology using advanced sensing modalities. Analytical Chemistry, 94(1), 327–337.