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https://doi.org/10.22239/2317-269X.02311

Organ-on-a-chip technology: assessing the global landscape of applicability in the regulatory context of pharmaceutical products

Tecnologia *organ-on-a-chip*: verificação do cenário global da aplicabilidade no contexto regulatório de produtos farmacêuticos

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Received: Mar 10, 2024
Approved: Jan 16, 2025

How to cite: Oliveira NR, Barroso WBG, Delgado IF. Organ-on-a chip technology: assessing the global landscape of applicability in the regulatory context of pharmaceutical products. Vigil Sanit Debate, Rio de Janeiro, 2025, v.13: e02311. https://doi.org/10.22239/2317-269X.02311

ABSTRACT

Introduction: Traditional preclinical studies using animals may not accurately reflect the efficacy and safety of compounds in humans. Therefore, the search for alternative methods and predictive strategies that offer advantages in terms of reliability, cost reduction, and ease of diffusion and adoption by laboratories is of great relevance, as well as ethical issues surrounding the use of animals. In this context, "organ-on-a-chip" (OoC) technology has been proposed as one of the alternatives to the use of laboratory animals. Although OoC technology is on the path to becoming widely accepted as a specific platform for preclinical research for human application and therapeutic testing, challenges and limitations remain to its regulatory acceptance. **Objective:** To address the technology's applicability and regulatory acceptance by comparing Brazil with the United States of America (USA) and the European Union (EU) based on registered patent applications, a literature review, and data from official websites. **Method:** Data was collected through searches in the CAPES portal of journals, the PatentScope database managed by the World Intellectual Property Organization (WIPO), the websites of regulatory agencies, companies that commercialize OoC, societies discussing this technology, and the TSAR tool. **Results:** Patents related to the fields of microfluidics, OoC, and microphysiological systems (MPS) have been filed. It was observed that pharmaceutical companies are evaluating and applying this technology, indicating that the market is likely to grow, although this technology is not yet included in official regulatory acceptance guidelines. **Conclusions:** These results demonstrate the potential to overcome the limitations of current models. However, to promote the inclusion of OoC as a globally recognized predictive method, mobilizing universities, industries, research centers, financial support institutions, and regulatory bodies in a collaborative effort is essential, combining scientific knowledge, regulatory guidelines, and investment in research and training.

KEYWORDS: Microphysiological System; Organ-on-a-Chip; Organs-on-Chip; Human on-a-Chip; New Approach Methods

RESUMO

Introdução: Os métodos tradicionais dos estudos pré-clínicos com animais podem não refletir com precisão a eficácia e a segurança de um composto em seres humanos. Assim, a busca por métodos alternativos e estratégias preditivas que se mostrem mais vantajosos em termos de confiabilidade, redução de custos e maior facilidade de difusão e incorporação pelos laboratórios é uma questão de grande relevância, bem como a discussão das questões éticas relacionadas ao uso de animais. Neste contexto, a tecnologia de "*organ-on-a-chip*" (OoC) vem sendo proposta como um dos métodos substitutivos ao uso de animais de laboratório. Embora a tecnologia de OoC esteja no caminho de se tornar amplamente aceita como uma plataforma específica para pesquisa pré-clínica para aplicação em humanos e na testagem terapêutica, ainda existem desafios e limitações para aceitação regulatória.

Objetivo: Abordar a tecnologia quanto à aplicabilidade e aceitação regulatória, comparando o Brasil com os Estados Unidos da América (EUA) e a União Europeia (EU), a partir dos pedidos de patentes registrados, revisão da literatura e dados de sites oficiais. **Método:** A pesquisa e coleta de dados foram realizadas por meio de buscas no acervo do portal de periódicos da CAPES, na base de dados *PatentScope gerenciada pela World Intellectual Property Organization* (WIPO), no site das agências reguladoras, das empresas que comercializam OoC, das sociedades que discutem essa tecnologia, e na ferramenta TSAR. **Resultados:** Verificou-se que foram depositadas patentes relacionadas a área de microfluídica, OoC e sistemas microfisiológicos (SMF). Observou-se que as indústrias farmacêuticas estão avaliando e aplicando essa tecnologia, indicando que o mercado tende a crescer, embora essa tecnologia ainda não esteja inclusa em guias oficiais para aceitação regulatória. **Conclusões:** Os resultados demonstram o potencial para suplantar as limitações dos modelos atuais. Porém, para promover a inclusão do modelo OoC como método preditivo reconhecido mundialmente, é imprescindível a mobilização conjunta de universidades, indústrias, centros de pesquisa, instituições financeiras de apoio e órgãos reguladores em um esforço colaborativo agregando conhecimento científico, diretrizes regulatórias e investimento em pesquisas e capacitação.

PALAVRAS-CHAVE: Sistemas Microfisiológicos; *Organ-on-a-Chip*; Órgãos em *Chip*; *Human-on-a-Chip*; Novas Abordagens Metodológicas

INTRODUCTION

Preclinical animal studies have limited predictive validity and may not accurately represent the efficacy and safety of a compound in humans, as indicated by the high failure rates of drugs in clinical trials[1,2]. Although massive investments have been directed towards developing analytical tools and standardizing animal studies, the drug approval rate remains low, with only 10% of Phase 1 candidates being approved by the Food and Drug Administration (FDA)[3]. It is estimated that around 30% of drugs fail in human clinical trials due to the occurrence of adverse reactions, while another 60% fail due to a lack of appropriate efficacy[4]. This results in high research and development (R&D) costs and delays in the introduction of potentially life-saving therapies, highlighting the need for pre-clinical models that are more robust, effective, and representative of human biology[3].

Companies are tackling this challenge by creating structures to integrate R&D organizations. One of the main focuses of this effort is the development of pre-clinical models that allow for a "fail early, fail fast" approach, which would result in candidate drugs with a higher probability of clinical success, greater patient safety, lower costs, and a faster time to market[2]. Pre-clinical trials with the experimental capacity to investigate and elucidate the mechanisms involved in pathophysiology, pharmacology, and toxicology are fundamental to the successful discovery and development of drugs[3,5].

Animal models offer the advantage of allowing the studying of systemic physiology, including tissue-specific distribution and metabolization processes, immune responses, microenvironmental influences, biological barriers, and interorgan interactions. However, the considerable phylogenetic distance between humans and model species introduces biological disparities—such as physiological variations and distinct disease manifestations—that can compromise translational relevance. These differences often limit the predictive accuracy of animal models, as they may fail to recapitulate human disease phenotypes or elicit expected therapeutic responses[3,6].

The search for alternative methods that are more advantageous in terms of reliability, cost reduction, and ease of dissemination and incorporation by laboratories is an issue of great relevance to biomedical research. In addition, it is essential to discuss ethical issues related to the use of animals[7]. The realization that experimental animals are sentient beings and that their use can contribute to the generation of knowledge must be accompanied by researchers applying the principles of the 3Rs ("reduction, refinement, replacement")[8].

In this context, the "New Approach Methods" (NAMs) are emerging as promising alternatives. The term covers a wide range of innovative approaches, without necessarily reflecting their stage of development or technological readiness. Among the methods included are Quantitative structure - Activity relationship (QSAR) prediction, large-scale screening bioassays, *omics* technologies, cell cultures, organoids, microphysiological systems (MPS), as well as machine learning and artificial intelligence (AI) tools, among others. These new approaches represent a greater capacity to elucidate toxicological outcomes and can significantly transform regulatory practices, making them more appropriate to human needs, both in the assessment of hazards and in the analysis of exposure to risks[9].

NAMs are accepted for the registration of pharmaceutical products by the Brazilian National Health Surveillance Agency (Anvisa), as long as they follow validated protocols and are conducted under the quality control conditions of Good Laboratory Practice - ISO 17.025 and properly designed considering the particularities of the product being tested[10].

This paper highlights organ-on-a-chip (OoC) technology among NAMs, which is included in the MPS category. It should be clarified that for an *in vitro* system to be classified as an MPS, it must necessarily surpass the simplicity of conventional two-dimensional cultures and may present various design elements, such as: a multicellular environment in a biopolymer or tissue-derived matrix, a three-dimensional organization, mechanical factors such as stretching or perfusion, the use of primary or stem cell-derived cells, and/or the inclusion of immunological components. In addition, many MPS systems incorporate vascular structures, as well as microfluidics, which simulate

natural tissue perfusion, allowing for the dynamic exchange of nutrients, hormones and cytokines[11]. This paper uses the term MPS only for systems with OoC microfluidics, although in the literature it is also applied to *in vitro* systems without flow, especially in models that mimic tissues without blood perfusion, such as cartilage or early embryonic stages[12]. In this context, OoCs are defined as microfluidic devices containing hollow microchannels perfused and coated with living cells, which reproduce physiology and pathophysiology at the organ level *in vivo* by recreating, *in vitro*, structures and functions that simulate tissue and organ functions[13].

The aim of this study is to analyze the technology in relation to its applicability and regulatory acceptance, comparing Brazil with the United States of America (USA) and the European Union (EU), based on registered patent applications, literature review, and data from official websites, illustrating some experiences and discussing some aspects in the regulatory context of pharmaceutical products for human use.

METHOD

This work was carried out in four distinct stages. The first stage was a literature review. For this search, controlled descriptors were used that had been previously defined by consulting the Health Sciences Descriptors (DeCS) of the Latin American and Caribbean Center on Health Sciences Information (Bireme)[14]. The terms selected in English were: "organ-on-a-chip" and "organs-on-chip". The selected descriptors were included based on keywords used by the researchers in the initial check of the literature to contextualize this work, "microphysiological system", and "human-on-a-chip", "new approach methods" and "organs-on-chip". The search was carried out on the journal portal of the Coordination for the Improvement of Higher Education Personnel (CAPES), from the available collection and in the subject search field.

In the second stage, a comprehensive search was conducted in the PatentScope database (World Intellectual Property Organization, WIPO)[15] using the most frequently recurring terms identified in the literature. The search strategy employed a combination of descriptors with the 'field combination' filter, and all retrieved results were considered for analysis." The following search strategy was used: EN_ALL: (microfluidic*) OR EN_ALL: (microphysiological) OR EN_ALL: ("*organ-on-a-chip*") OR EN_ALL: ("*organ-on-chip*") OR EN_ALL: ("*tissue-chip*") OR EN_ALL: ("*human-on-chip*") OR EN_ALL: ("*human-on-a-chip*") OR EN_ALL: ("*tissue chip*"). In addition, a search with text in Portuguese was included, PT_ALL: ("órgãos em chip") OR PT_ALL: ("*organ on chip*"), PT_ALL: (*microfluidic**) OR PT_ALL: (*Microfisiologic**) OR PT_ALL: ("órgãos em chip") OR PT_ALL: ("tecidos em chip") OR PT_ALL: ("mimet* tecido biológico") e PT_ALL: ("dispositivo microfluídico") to search for patents filed in Brazil. The patents identified refer to the generation of OoC devices and other apparatus claimed to be applicable to this technology. This search guided the next steps, focused on geographical areas with the highest number of patents filed and with the highest number of disclosures through interested parties gathered in associations and/or societies. The areas that meet these two criteria are the United States and the European Community. We excluded Canada, Asia, Oceania, and the United Kingdom, whose data was collected separately, according to the methodology employed and described.

In the third stage, a search was carried out on the official websites of regulatory agencies, legally authorized companies to research and market OoC device platforms, and societies created to disseminate and share information about organs-on-chip.

Finally, the European Community's Tracking System for Alternative Methods Towards Regulatory Acceptance (TSAR)[16] search tool was used to see if there were any records on the validation of OoC technology submitted by validation centers or official bodies. The filters "Test Method Name / Short name" and "Responsible Organization" were used.

Brazil is included in this study because it is the subject of this article's critical analysis. Therefore, searches were carried out focusing on the scientific production of researchers working in the field and a general search on the Google platform for news of institutions carrying out OoC studies in the country.

This search was not exhaustive, as it was limited to the descriptors mentioned and the geographical areas chosen. The search was not limited to a specific period, as the technology is recent, and we sought to retrieve as much information as possible.

RESULTS AND DISCUSSIONS

Literature review

The literature search contextualized this work and showed that OoC technology has emerged due to the convergence of tissue engineering and microfabrication, proving to be a potential alternative to traditional preclinical models in the study of organ and tissue functions, as well as in testing the safety and efficacy of drugs[17].

Our results show numerous review articles presenting the impact of microfluidics in the testing of anticancer drugs[5,3,17,18,19,20] and in the use of blood-brain barrier models[3,5,11,17,18,20,21] for drug screening. In addition, pioneering studies have presented OoC platforms with brain-on-chip[5,11,17,18,20,21,22,23,24], heart-on-chip[5,17,18,20,21,25,24], liver-on-chip[3,5,11,17,18,20,21,24,26,27,28], kidney-on-chip[3,5,11,17,18,20,21,24,29], lung-on-chip [5,11,17,18,20,21,24,29], intestine-on-chip[17,18,26,27,5,20,29,21], blood vessels-on-chip[5,11,17,18,20,21,30,31].

OoC technology was first developed in 2010. This first model reconstituted the organ-level functions of the lung and was developed by the Wyss Institute for Biologically Inspired Engineering at Harvard University, USA[32]. Organs on a chip are also defined as three-dimensional (3D) cell culture tissues configured in a microfluidic device (the "chip") that contain

natural or engineered tissues[33,34]. They are called "chips" because they were initially manufactured using micromanufacturing methods adapted from the production of computer microchips[13]. These systems, which reproduce the functions of human organs, allow for a more accurate assessment of tissue response to pharmacological compounds. The devices can be made from silicone rubber, such as polydimethylsiloxane (PDMS), glass or thermoplastics, such as poly(methyl methacrylate) (PMMA). The choice of device material depends on numerous factors, including functionality, manufacturing strategy, and biocompatibility[34].

OoC microfluidic devices are tailored to replicate the cellular and extracellular characteristics of organs that can respond to physical and biochemical signals to maintain and simulate organ function, with the potential to replace *in vivo* animal tests[34]. These advances seek to model the pathophysiology of the human body and systemic diseases, producing tissues with their phenotype preserved to communicate physiologically. There are already reports in the literature of the development and applicability of integrated devices, identified as "tissue chips"[35], "human-on-a-chip"[36], and "body-on-a-chip"[18]. Some studies have shown promising results in the creation and testing of human models in microfluidic systems for specific diseases, such as pulmonary arterial hypertension[37], opioid overdose[38], and non-alcoholic fatty liver disease[39] and other liver diseases[3], various types of cancer[3], diabetes[3], hepatitis B virus (HBV)[3], hepatitis C virus (HCV)[3], renal fibrosis[3], viral respiratory diseases[3], and drug-induced nephrotoxicity[3]. When it comes to toxicity and chemical risk, the assessment of absorption, distribution, metabolism, and excretion (ADME/biokinetics) has faced challenges, including false positive in *in vitro* results leading to the need for more careful observations[10].

However, the technology described is an innovation that is still being developed and validated for different applications[3]. Regulatory acceptance is still limited, but its use has been expanding in the pharmaceutical, chemical and cosmetics industries[34], including new studies in quality control, such as potency studies of medicines and biological products[40,41,42].

Brazil has demonstrated a significant commitment to promoting alternative methods to the use of animals in research. As part of this effort, the Ministry of Science, Technology and Innovation (MCTI) created the Brazilian National Network of Alternative Methods (RENAMA) in July 2012. Soon after, in September of the same year, the Brazilian Center for the Validation of Alternative Methods (BraCVAM) was established, the result of a collaboration between Anvisa and the National Institute for Quality Control in Health (INCQS) of the Oswaldo Cruz Foundation (Fiocruz). These pioneering initiatives in Latin America were designed to coordinate efforts and promote alignment with the principles of the 3Rs in scientific research[6].

Patent applications filed

The data retrieved showed that the patent applications filed were classified into different areas of knowledge, including chemistry and physics, and others. Therefore, the result reflects all applications within microfluidics, MPS, support for tissue growth, as well as organs on a chip. The number of patents filed by geographical area, considering the top 10 countries in the ranking and the year of publication, according to the PatentScope[15] database, is shown in Figure 1. The geographical areas identified by the search include USA, European Patent Office (EPO), Canada (CAN), Australia (AUS), China (CHN), India (IND), United Kingdom (UK), Republic of Korea (ROK), and Singapore (SGP). Patents filed with an international application, through the Patent Cooperation Treatment (PCT), also appeared in the searches.

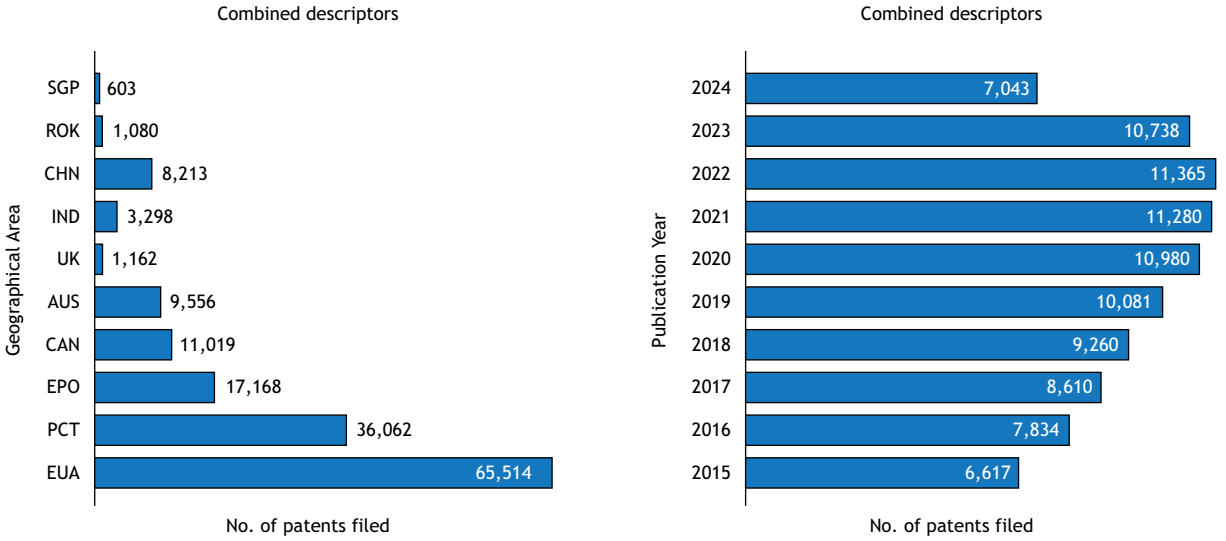
Figure 1 also shows that the number of patent applications has increased over the years: in 2015, 6,617 patent applications were filed, while in 2023 this figure rose to 10,738. Up until the last consultation, held on September 25, 2024, the number of applications filed was 7,043[15].

In an initial search, only two patent applications were found in Brazil: one filed by the German company *TissUse GmbH*, in 2017, and another by *Sociedade Beneficente Israelita Brasileira Hospital Albert Einstein*, in 2018[15]. Due to the limited number of results, the search field was expanded to include terms in Portuguese, which made it possible to identify four more patent applications: two filed jointly by the Brazilian Center for Research in Energy and Materials (CNPEM) and the State University of Campinas (Unicamp), in 2019 and 2020; one by CNPEM, separately, in 2019; and another by Unicamp, also separately, in 2021[15]. This brings the total number of patent applications found in Brazil to six.

The interest in advancing OoC technology is evident from the number of patents filed. In general, patents, by offering legal protection and temporary exclusivity over an invention, motivate inventors to disclose their discoveries publicly in exchange for the right to commercial exploitation. As a result, new ideas can be developed, thus promoting the progress of science and technology. However, since many OoC devices can be easily copied by reverse engineering, it is more efficient to protect tissue compositions, culture media, hardware, and software by intellectual property[33].

Experience in the European Union

In Europe, joint efforts between governments, industries, and universities have driven the development of alternative methods to animal experimentation, with a focus on toxicity[33]. A milestone was the meeting of experts in Leiden, Netherlands, which highlighted the need for robust protocols to increase regulatory acceptance of these methodologies, especially for interspecies differences and quantitative *in vitro-in vivo* extrapolations. The creation of a specialized biokinetics group by the Organization for Economic Co-operation and Development (OECD) was suggested to oversee these advances, including modeling of transporter-mediated processes and the development of cellular models that accurately mimic the physiology and kinetic characteristics of organs[43].



Source: Prepared by the authors based on the search results in WIPO - *Search:* https://patentscope.wipo.int/search/en/structuredSearch.jsf.

Figure 1. Number of patents filed by geographical area and number of patents published per year.

The Organ-on-Chip in Development (ORCHID) project, which began in 2017 and ended in 2019, sought to create a roadmap for OoC technology and foster collaboration between stakeholders. This project generated a report highlighting that this technology could bridge the gap between pre-clinical tests and human clinical trials through more predictive models[44]. This document also demonstrated the potential of this technology to reduce R&D costs, increase success rates and shorten the development time of new drugs. It also identified the need to train technicians and end users to promote qualification and adoption of the technology.

According to the study, immediate implementation of the technology in the R&D environment and acceptance by regulatory agencies are still the main barriers to implementing the technology[44].

As an offshoot of ORCHID, The European Organ-on-Chip Society (EUROoCS) was created in 2018[44]. This non-profit organization brings together members from various sectors - government, academia, the pharmaceutical industry, cosmetics, chemistry, health foundations, and the general public - to encourage OoC research and align technology with regulatory requirements[45].

Other working groups discuss the absence of specific guidelines for human cell-based *in vitro* methods in the OECD guides, such as acute toxicity and neurotoxicity. They suggest integrating OoCs with mechanisms based on biological events, known as Adverse Outcome Pathways (AOPs), prioritizing organs affected by chemical and pharmaceutical products. In addition, it is recommended to combine safety data from sources such as *in chemico*, *in vitro*, *in vivo*, and *omics* technologies, using strategies such as Integrated Approaches to Testing and Assessment (IATAs)[33,43].

Experience in the United States

In 2010, the American Institute of Biomedical Research and Public Health Fund, the National Institutes of Health (NIH), announced a collaboration with the American regulatory agency, the FDA, to advance regulatory science through a program that included a project to develop tissue models of the heart and lung on a *chip* to test the safety and efficacy of drugs[46].

In 2012, the National Center for Advancing Translational Sciences (NCATS) initiated the Tissue Chip for Drug Screening program, which funded 12 projects to create 3D human organ systems capable of representing physiological interactions. Subsequently, researchers expanded these efforts by developing multiple organ-on-chip models that simulate interactions between different systems[46].

Strategic partnerships have been established, such as NCATS' collaboration with the Center for the Advancement of Science in Space (CASIS) in 2016 to explore the effects of microgravity on organ and tissue-on-chip platforms. The experiments were carried out at the International Space Station U.S. National Laboratory to better understand diseases and their impact on human health.

Additionally, NCATS acted to pave the way for independent testing and validation of these platforms with the aim of ensuring the availability and promoting the adoption of this technology to the scientific community, particularly among regulatory agencies and pharmaceutical industries[46].

In 2020, the development of bioengineered models of human tissue and organ systems for clinical trials served as support during the COVID-19 pandemic. Researchers used their *expertise* in *tissue chips* to evaluate the properties of SARS-CoV-2, the pathology itself, and the use of various drugs and therapies against

COVID-19 infection[46]. The pandemic context has highlighted the need for new models, with greater predictive capacity, to accelerate advances in the pharmaceutical field[9].

The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) MPS Affiliate, an international non-profit consortium of around 48 companies, including AstraZeneca, Pfizer, Sanofi, GSK, Moderna Therapeutics, Biogen, and Bayer, is working to integrate MPS into drug safety approaches. This group promotes the appropriate characterization of these models, demonstrating their transformative potential[47].

Through the FDA's Innovative Science and Technology Approaches for New Drugs (ISTAND) program, a study analyzed nearly 800 human liver *chips*, created with cells from two different donors. The chips successfully met the IQ consortium's liver toxicity qualification guidelines, using a blinded set of more than 27 drugs known to be hepatotoxic and non-toxic, achieving a sensitivity of up to 87% and specificity of 100%. These results represent an improvement in performance compared to animal models[48].

The approval of the FDA Modernization Act 2.0 in 2021 marked a significant step forward in the adoption of alternative technologies, signaling the importance of validating MPS and *in silico* approaches. This act opened new opportunities to incorporate these technologies into drug regulatory processes[49].

In 2022, a regulatory milestone was reached with FDA authorization for clinical trials aimed at approving two new uses of a drug, in which the simulation of two rare neuromuscular diseases was based on 3D models. The system, made up of motoneurons and Schwann cells, provided essential pre-clinical data for approval. The project was partially funded by NCATS, highlighting the potential of these technologies in the study of rare diseases that do not yet have effective treatments, for which animal models are often lacking[50].

Experience in Brazil

In Brazil, there are some specific initiatives taking place in universities, foundations, industries and experimental research centers.

A successful evaluation of therapeutic efficiency was carried out at the Experimental Research Center (CPE) and the *Instituto Israelita de Ensino e Pesquisa Albert Einstein* (IIEP – Einstein's Teaching and Research Institute) of the Albert Einstein Hospital in São Paulo. The aim was to evaluate magneto-hyperthermia therapy with glioblastoma tumors-on-chip[51].

In 2017, researchers from the University of São Paulo's São Carlos Chemistry Institute published an article on a promising methodology for producing a microfluidic device that mimics a blood vessel, serving as a starting point for cell culture under perfusion for cardiovascular research and cardiotoxicity studies[52].

This same institute is involved in research related to the development of microchip systems, as demonstrated in an article published in 2021 on the effect of "shear stress" (tangential force exerted by fluid flow) on endothelial cells[53].

In 2016, the CNPEM website announced the transfer of cell culture technology on a chip from the German startup *TissUse GmbH* to the National Biosciences Laboratory (LNBio), which is linked to the Ministry of Science, Technology and Innovation (MCTI). Also taking part in this initiative was the *O Boticário* Group, which, as well as providing financial resources, contributed scientific and technological knowledge to the project[54].

Another cosmetics company is emerging on the "human-on-a-chip" scene, *Natura* in partnership with LNBio, as announced on the CNPEM website in March 2023. The company uses 3D printed organs for testing, combining biological structures equivalent to human and integrated organs, which makes it possible to reproduce the functioning of the organism. This allows researchers and scientists to evaluate the effects of a cosmetic ingredient both inside (organs) and outside the body (skin) simultaneously[55].

Other important studies have been carried out by LNBio applying OoC platforms (called 2-OC, emulating liver and intestinal functions) to characterize the pharmacokinetic and toxicological properties of acetaminophen. The results showed that the intestinal absorption and hepatic metabolism of the study drug can be mimicked by MPS and that the association with *in silico* methods can improve the predictive capacity of *in vitro* methods and improve the accuracy of the tests when compared to studies in animal models[26,27].

A detailed study on OoC mimicking bone marrow cells was conducted by researchers from the Federal University of Minas Gerais, the Federal University of the Jequitinhonha and Mucuri Valleys, and the René Rachou Institute of the Oswaldo Cruz Foundation, which demonstrated that OoC technology has been widely applied in bone marrow studies for various purposes: biological behavior of marrow cells, modeling marrow diseases, mimicking the marrow niche, and drug testing. The results showed that the methods selected in the publications evaluated in the study improved cell culture maintenance, long-term culture, cell behavior, cell process, and cell response to drugs compared to conventional static 2D and 3D culture. However, despite these satisfactory results, bone marrow reproduction has several structural and physiological limitations[56].

As far as validation is concerned, the process in Brazil follows OECD guidance document 34 and BraCVAM acts as a focal point for identifying and/or receiving requests from parties interested in submitting tests for validation. The Centre then informs RENAMA of promising tests, which helps with prioritization and contributes to validation studies of selected tests in the network's laboratories. The validation studies are supervised and the results obtained are reviewed by an *ad hoc* scientific committee. Based on the results of the peer review, BraCVAM prepares recommendations on the validated test method, which will be sent to the National Council for the Control of

Animal Experimentation (CONCEA) for regulatory adoption, following a public consultation[57].

Also in the regulatory context, on August 31, 2022, Anvisa held a lecture entitled "Human-on-a-Chip", in conjunction with the Brazilian Agency for Industrial Development (ABDI) and one of RENAMA's central laboratories, LNBio, with the focus on presenting methodology and the possibility of in-depth study of diseases, as well as new drugs, through the use of technological resources in human cell cultures[36]. Regarding OoC registration regulations, based on the webinar on alternative methods to the use of animals and their regulatory acceptance in the field of medical devices held on September 15, 2022, Anvisa pointed out that the use of the OoC model is not yet a reality in the biological safety assessment of medical devices (drugs are not included in this class)[58].

CONCEA's position obtained in response to an official consultation with the body

To date, no request for approval of the OoC test has been identified at CONCEA. However, if any research shows consistent data from tests that demonstrate scalability, standardization, reproducibility and repeatability between and among laboratories, a request for validation of the method can be made to CONCEA, which in turn will forward the request to RENAMA for analysis by the associated laboratories. If the request is approved, CONCEA will validate the test as an alternative method to the use of laboratory animals[57].

As such, the OoC method has not yet been recognized as an alternative method to the use of animals by CONCEA, according to item II of Article 2 of Decree No. 6,899 of July 15, 2009. However, according to Article 5 of CONCEA's Normative Resolution (NR) 54: "Alternative methods validated nationally or internationally, but not yet recognized by CONCEA, may be used, without prejudice to the competence provided for in item III of Art. 5 of Law 11.794, of October 8, 2008". Therefore, although CONCEA has not yet recognized any MPS or microfluidic device and has not yet included any chapter on this new technology in its guide[8], it can be used (once it complies with special rules issued by other public entities and bodies with regulatory competence) in convergence with the 3Rs principle that underpins CONCEA's deliberations.

Highlights in the OoC technology knowledge landscape over time

Since the publication in 2010 of the development of a microdevice that reproduced the main properties of the human alveolar-capillary interface and introduced the concept of OoC, knowledge of the technology has spread beyond university laboratories[32]. The research carried out enabled a timeline to be drawn up with the main highlights of this scenario, as shown in Figure 2.

Adoption of OoC platforms in pharmaceutical industries

The study by Vulto and Joore[59] demonstrates that the available literature shows that OoC technology is being analyzed and used by the pharmaceutical industries, and, to this end, they are investing in the implementation of platforms, quality control standards, the availability of robust testing protocols, and the logistics of biological materials. The Table represents a summary of the commercially available platforms, impacting decision-making in the various phases that cover the pre-clinical development of a drug.

Method recognition

The TSAR tool checks whether there are methods that have reached the criteria for regulatory acceptance as alternatives to the use of animals, and are recognized for application in various sectors, accompanied by a summary description. When available, TSAR also includes relevant records and documents associated with each method, covering different stages of the process: submission, validation, peer review, recommendations, and regulatory acceptance, including international standards represented in the tracking system[16].

In this search, no tests were found that could be established as platforms that use MPS, especially OoC.

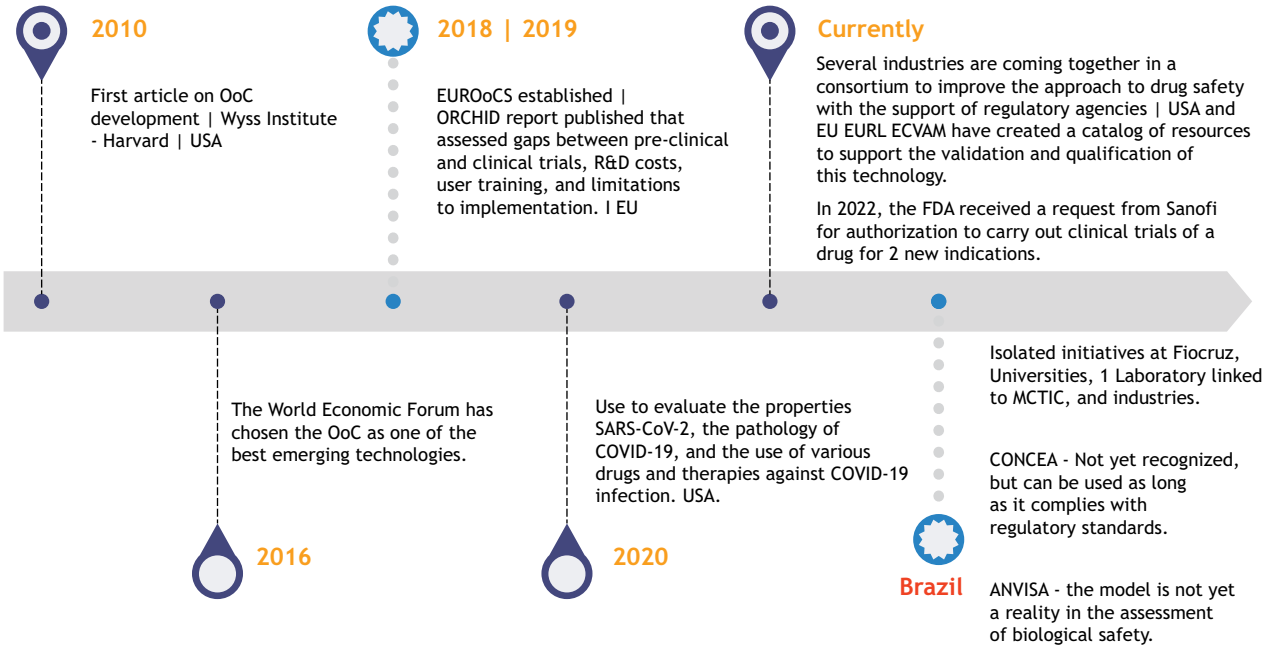
Future prospects and challenges for implementing the technology

According to the NIH, the implementation of tissues on a chip in the development of drugs in the program for the approval and use of organs on a chip involves the effective action of developers and suppliers of the technology, representatives of the pharmaceutical industry, regulatory agencies, other government entities, and patient groups[4,60].

The development of OoC, which is moving towards becoming part of regulatory safety assessment, can benefit significantly from the regular stakeholder interactions[5] highlighted in Figure 3.

The program also highlights the actions needed for the technology to be widely used. These actions include demonstration and validation for toxicity and safety studies; the establishment of testing centers and databases; demonstration and validation for modelling and efficacy studies in common and rare diseases; adoption and use by drug developers; global harmonization for regulatory use and standardization of MPS platforms; training of future generations of scientists in MPS and regulatory qualification as a tool for drug development and even clinical trials on chip[60].

Despite the progress made, the engineering of human tissues in three dimensions (3D) to make organ equivalents (at different scales and for various purposes), as well as microfluidic and MPS devices, are still in the development phase. This technology faces significant challenges, including: the availability of cell types, adaptability, and the most appropriate choice of cell source. In addition, optimizing the formulation of the culture medium for different cell types is crucial. It is also essential to understand the distribution of drugs in organs, diffusion



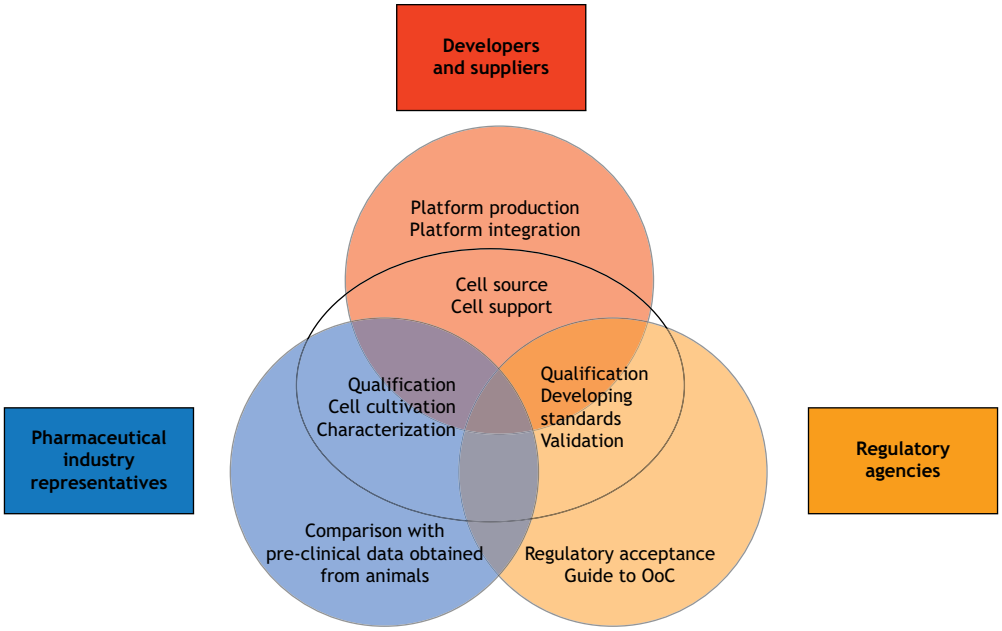
Source: Prepared by the authors.

Figure 2. Some highlights in the OoC technology recognition evolution scenario.

Table. Impact of commercial OoC platforms on the industry.

PHARMACEUTICAL INDUSTRY	TARGET ORGAN	OoC DEVELOPER
Target identification and validation		
Novo Nordisk	Blood vessels	MIMETS
AstraZeneca	Liver and pancreas	TissUse
Discovery	Blood vessels	MIMETS
Galapagos	Blood vessels	MIMETS
Galapagos	Intestine	
Roche	Intestine	MIMETS
Pharmacokinetics and Pharmacodynamics		
Astellas	Proximal renal tubule, blood vessels	MIMETS
AstraZeneca	Liver	Emulate
Pre-clinical safety		
Roche	Liver	Emulate
Roche	Intestine	Emulate
Janssen, AstraZeneca	Liver	Emulate
AstraZeneca	Bone marrow	Emulate
AstraZeneca, Roche, Bayer	Bone marrow	TissUse
Bayer	Liver, thyroid	TissUse
Bayer	Skin tumor	TissUse
Clinical development		
Roche	Intestine	MIMEIAS

Source: Prepared by the authors based on Adoption of Organ-on-chip Platforms by the Pharmaceutical Industry[59].



Source: Prepared by the authors based on the NIH presentation at the Emulate: How Government Funding Spurs Scientific Innovation webinar[60].

Figure 3. Summary of NHI's Tissue Chips program in collaboration with FDA, NCATS and Defense Advanced Research Projects Agency (DARPA), industries, developers, and suppliers with their respective activities.

distances and metabolic rates to emulate *in vivo* communication between organs[6].

Still discussing challenges, EUROoCS presented a list of them, as well as opportunities for the development of OoC technology[45] and the need to meet regulatory requirements for acceptance and validation by agencies, as shown in Figure 4.

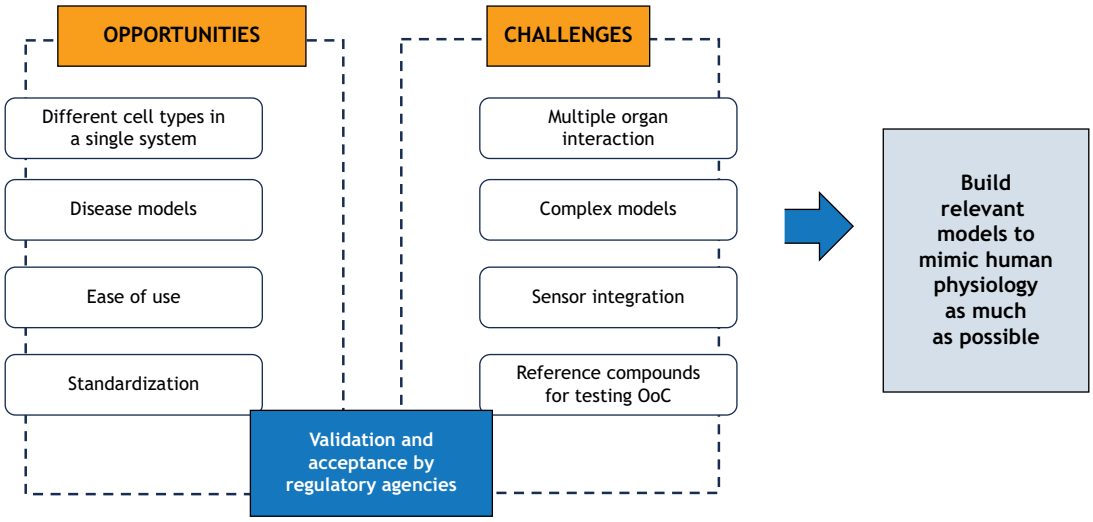
Research aimed at the quality control of biological products has been emerging for potency studies that meet the guidelines of the World Health Organization (WHO). Microfluidic devices have been showing results that demonstrate the potential to improve the evaluation of the bioactivity of mesenchymal cells and their influence on vasculogenesis, and of botropic antivenom, to neutralize snake venom. This is particularly relevant for overcoming the limitations of conventional analytical methods in capturing functional potency[40,42].

A study was recently published on the use of OoC in the field of phyto-nanomedicine for the treatment of osteoarticular diseases. The results showed that these models allow precise control and high-throughput screening to identify phytoconstituents for release through nanoparticles, effective from complex plant extracts, with minimal sample requirements compared to conventional methods[41].

A more up-to-date perspective recognizes that an equivalence of approaches accepted from a regulatory point of view generally does not imply the direct replacement of one test by another. Instead, it is understood that it is necessary to integrate all available information so that it complements existing approaches, providing a more comprehensive and detailed understanding of possible adverse effects[10]. This view reflects the growing appreciation of alternative and complementary methodologies to better assess the safety and efficacy of products, minimizing the use of traditional models.

The studies also highlight the following challenges for implementation:

- Standardization: ensuring the uniformity of cells and tissues, as well as compatibility with the device's manufacturing materials[33].
- Validation: the complexity of the process. The conventional method, which compares the results of the new method with the "old" one, is inadequate, as it does not cover all toxicity tests and companies often develop specific devices. Furthermore, validation involves a long process of standardization and harmonization of the method, which is necessary for its inclusion in technical guides, such as those from the OECD[33].
- Intellectual property: the OECD is reluctant to accept guidelines that include models protected by intellectual property, to avoid creating monopolies in the industry[33].
- Costs: the development of devices and the transition from prototypes to large-scale production, depending on the material used, can require high investments[33].
- Other challenges: the preference for primary cells over immortalized lineages, as well as logistical difficulties in supplying human cells. Ethical issues also emerge,



Source: Prepared by the authors based on the EUROoCS Portal[45].

Figure 4. List of opportunities and challenges and interaction with regulatory agencies, according to EUROoCS.

especially in the use of embryonic stem cells and the possibility of multi-organ systems mimicking the human body so accurately that they can be considered life forms, raising complex ethical dilemmas. This point becomes particularly relevant in the face of technological advances that connect organ modules by vascular perfusion, forming a "body-on-a-chip", recreating interactions between organs, physiological relationships, metabolic pathways, significant biological barriers, and complete body responses to drugs, in a manner similar to what occurs *in vivo*[18,33].

To overcome these barriers, it is crucial to develop coordinated human tissue supply chains and resolve ethical issues related to the use of donated organs and informed consent[33].

OoC market

The World Economic Forum classified this technology as one of the most promising in 2016, highlighting its transformative potential for the pharmaceutical industry[34].

A study carried out on the OoC market estimated that the market value in 2024 will be approximately 0.30 billion dollars, with a growth forecast to reach 1.15 billion by 2029, with North America being the largest market[61]. Nevertheless, this region is the geographical area with the highest number of patents filed[15]. The FDA regulatory agency, acting as a non-financial partner, has been active as a catalyst, improving communication between stakeholders and disseminating information through projects in regulatory science, advances in scientific knowledge, as well as other support activities[60].

The advance of the market is motivating, but the potential of OoC models for regulatory acceptance depends on the opportunities created to expand and develop initiatives that generate consistent results that demonstrate the efficacy of the trials, and, in this sense, the aforementioned model of active action by the FDA, providing regulatory direction, is an example that can be followed by other regulatory agencies.

CONCLUSIONS

The use of OoC models represents a significant innovation in drug development, allowing biological interactions to be simulated in controlled environments. This technology has the potential to generate results comparable to the reactions observed in human beings. The scientific literature already presents a large number of studies, particularly in the toxicological field, highlighting the predictive potential and applicability of these devices as an alternative to animal experimentation.

For regulators to feel confident about accepting the test results described in the product registration and/or maintenance of conformity processes, the results must be robust. In addition, the description and execution steps of the tests must be in line with recognized quality requirements. This depends on the use of validated methods, with properly planned experiments that consider the specificities of the product being tested.

Although OoC technology is on its way to becoming widely accepted as a human-specific experimental platform for pre-clinical research and therapeutic testing, there are still challenges to overcome and limitations related to method validation, costs, scalability, reproducibility, standardization, intellectual property, ethical issues related to the use of embryonic stem cells and multi-organ systems, and regulatory approval. In the global context, especially in the US and Europe, the adoption of this technology has advanced, driven by consistent collaborative initiatives between industries, research centers and government agencies that have

been generating data to support validation actions and the establishment of regulatory requirements.

Collaboration between stakeholders is essential, and, in this sense, sending data to regulatory agencies generated from OoCs highlights the promising potential of the model, which is corroborated by the upward trend observed in market analysis and patent filings.

In view of this, Brazil, despite its rich intellectual capital in research, needs to organize itself institutionally and advance in cooperation with different entities, aligning itself with international initiatives. This is essential to boost research and expand the opportunities related to OoC technology, allowing the country to position itself as a leader in translational research in Latin America.

REFERENCES

1. Mittal R, Woo FW, Castro CS, Cohen MA, Karanxha J, Mittal J et al. Organ on chip models: implications in drug discovery and clinical applications. J Cell Physiol. 2019;234(6):8352-80. https://doi.org/10.1002/jcp.27729
2. 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(1):1-16. https://doi:10.1038/s43856-022-00209-1
3. Irrechukwu O, Yeager R, David R, Ekert J, Saravanakumar A, Choi CK. Applications of microphysiological systems to disease models in the biopharmaceutical industry: opportunities and challenges. Altex. 2023;40(3):485-518. https://doi.org/10.14573/altex.2204071
4. Tagle DA. The NIH microphysiological systems program: developing in vitro tools for safety and efficacy in drug development. Curr Opin Pharmacol. 2019;48:146-54. https://doi.org/10.1016/j.coph.2019.09.007
5. Wang Y, Gao Y, Pan Y, Zhou D, Liu Y, Yin Y et al. Emerging trends in organ-on-a-chip systems for drug screening. Acta Pharm Sin B. 2023;13(6):2483-509. https://doi.org/10.1016/j.apsb.2023.02.006
6. Marin TM, Pagani E. Sistemas microfisiológicos compostos por organoides humanos em dispositivos microfluídicos: avanços e desafios. Vigil Sanit Debate. 2018;6(2):74-91. https://doi.org/10.22239/2317-269X.01053
7. Abreu CLC, Presgrave OAF, Delgado IF. Metodologias alternativas à experimentação animal: aplicação no controle da qualidade de produtos sujeitos à ação da vigilância sanitária. Rev CFMV. 2008;14(45):15-23.
8. Ministério da Ciência, Tecnologia e Inovação (BR). Guia brasileiro de produção, manutenção ou utilização de animais em atividades de ensino e pesquisa científica. Brasília: Conselho Nacional de Experimentação Animal; 2023[acesso 1 jun 2023]. Disponível em: https://www.gov.br/mcti/pt-br/composicao/conselhos/concea/paginas/publicacoes-legislacao-e-guia/guia-brasileiro-de-producao-manutencao-ou-utilizacao-de-animais-para-atividades-de-ensino-ou-pesquisa-cientifica
9. Schmeisser S, Miccoli A, Von Bergen M, Berggren E, Braeuning A, Busch W et al. New approach methodologies in human regulatory toxicology: not if, but how and when! Environ Int. 2023;178:1-40. https://doi.org/10.1016/j.envint.2023.108082
10. Villela IV, Machado MDS. Brazil's regulatory context for using new approach methodologies (NAMs) on the registration of products. Front Toxicol. 2022;4:1-6. https://doi.org/10.3389/ftox.2022.903027
11. Peterson NC, Mahalingaiah PK, Fullerton A, Di Piazza M. Application of microphysiological systems in biopharmaceutical research and development. Lab Chip. 2020;20(4):697-708. https://doi.org/10.1039/C9LC00962K
12. Marx U. Biology-inspired microphysiological systems to advance medicines for patient benefit and animal welfare. Altex. 2020;37(3):365-94. https://doi.org/10.14573/altex.2001241
13. Sontheimer-Phelps A, Hassell BA, Ingber DE. Modelling cancer in microfluidic human organs-on-chips. Nat Rev Cancer. 2019;19(2):65-81. https://doi.org/10.1038/s41568-018-0104-6
14. Organização Panamericana de Saúde – OPAS. Descritores em ciência da saúde DeCS/MeSH. Biblioteca Virtual em Saúde. 2023[acesso 28 ago 2023]. Disponível em: https://decs.bvsalud.org/.
15. World Intellectual Property Organization – WIPO. Patentscope simple search. Geneva: World Intellectual Property Organization; 2024[acesso 25 set 2024]. Disponível em: https://patentscope.wipo.int/search/pt/search.jsf
16. European Commission – EC. Tracking system for alternative methods towards regulatory acceptance (TSAR). Brussels: European Commission; 2024[acesso 16 jan 2024]. Disponível em: https://tsar.jrc.ec.europa.eu/
17. Feng J, Neuzil J, Manz A, Iliescu C, Neuzil P. Microfluidic trends in drug screening and drug delivery. Trends Analyt Chem. 2023;158. https://doi.org/10.1016/j.trac.2022.116821
18. Monteduro AG, Rizzato S, Caragnano G, Trapani A, Giannelli G, Maruccio G. Organs-on-chips technologies: a guide from disease models to opportunities for drug development. Biosens Bioelectron. 2023;231:1-38. https://doi.org/10.1016/j.bios.2023.115271

19. Zuchowska A, Skorupska S. Multi-organ-on-chip approach in cancer research. Organs On Chip. 2022;4:1-10. https://doi.org/10.1016/j.ooc.2021.100014

20. 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. https://doi.org/10.1016/j.tips.2020.11.009

21. Ahmed T. Organ-on-a-chip microengineering for bio-mimicking disease models and revolutionizing drug discovery. Biosen Bioelectr X. 2022;11:1-29. https://doi.org/10.1016/j.biosx.2022.100194

22. Hogberg HT, Smirnova L. The future of 3D brain cultures in developmental neurotoxicity testing. Front Toxicol. 2022;4:1-8. https://doi.org/10.3389/ftox.2022.808620.

23. Romero JC, Berlinicke C, Chow S, Duan Y, Wang Y, Chamling X et al. Oligodendrogenesis and myelination tracing in a Crispr/Cas9-engineered brain microphysiological system. Front Cell Neurosci. 2023;16:1-17. https://doi.org/10.3389/fncel.2022.1094291

24. Seidi S, Eftekhari A, Khusro A, Heris RS, Sahibzada MUK, Gajdács M. Simulation and modeling of physiological processes of vital organs in organ-on-a-chip biosystem. J King Saud Univ Sci. 2022;34(1):1-16. https://doi.org/10.1016/j.jksus.2021.101710

25. Vivas A, Van Den Berg A, Passier R, Odijk M, Van Der Meer AD. Fluidic circuit board with modular sensor and valves enables stand-alone, tubeless microfluidic flow control in organs-on-chips. Lab Chip. 2022;22(6):1231-43. https://doi.org/10.1039/d1lc00999k

26. Marin TM, Indolfo NC, Rocco SA, Basei FL, Carvalho M, Gonçalves KA et al. Acetaminophen absorption and metabolism in an intestine/liver microphysiological system. Chem Biol Interact. 2019;299:59-76. https://doi.org/10.1016/j.cbi.2018.11.010

27. Marin TM, Indolfo NDC, Rocco SA, Carvalho M, Dias MM, Bento GIV et al. An intestine/liver microphysiological system for drug pharmacokinetic and toxicological assessment. J Vis Exp. 2020;(166). https://doi.org/10.3791/60184-v

28. Rubiano A, Indapurkar A, Yokosawa R, Miedzik A, Rosenzweig B, Arefin A et al. Characterizing the reproducibility in using a liver microphysiological system for assaying drug toxicity, metabolism, and accumulation. Clin Transl Sci. 2021;14(3):1049-61. https://doi.org/10.1111/cts.12969

29. Tang H, Abouleila Y, Si L, Ortega-Prieto AM, Mummery CL, Ingber DE et al. Human organs-on-chips for virology. Trends Microbiol. 2020;28(11):934-46. https://doi.org/10.1016/j.tim.2020.06.005

30. Santos Rosalem G, Gonzáles Torres LA, De Las Casas EB, Mathias FAS, Ruiz JC, Carvalho MGR. Microfluidics and organ-on-a-chip technologies: a systematic review of the methods used to mimic bone marrow. PLoS One. 2020;15(12):1-31. https://doi.org/10.1371/journal.pone.0243840

31. Lam J, Yu J, Lee B, Campagna C, Yoo S, Baek K et al. Characterizing on-chip angiogenesis induction in a microphysiological system as a functional measure of mesenchymal stromal cell bioactivity. Adv Biol (Weinh). 2024;8(8). https://doi.org/10.1002/adbi.202300094

32. 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. https://doi.org/10.1126/science.1188302

33. Heringa MB, Park MVDZ, Kienhuis AS, Vandebriel RJ. The value of organs-on-chip for regulatory safety assessment. Altex. 2019;37(2):208-22. https://doi.org/10.14573/altex.1910111

34. Leung CM, Haan P, Ronaldson-Bouchard K, Kim GA, Ko J, Rho HS et al. A guide to the organ-on-chip. Nature Rev. 2022;2. https://doi.org/10.1038/s43586-022-00118-6

35. 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. https://doi.org/10.1038/s41551-022-00882-6

36. Agência Nacional de Vigilância Sanitária - Anvisa. Especialista fará palestra sobre órgãos em chips. Brasília: Agência Nacional de Vigilância Sanitária; 2016[acesso 28 ago 2023]. Disponível em: https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2016/especialista-fara-palestra-sobre-orgaos-em-chips

37. Al-Hilal TA, Keshavarz A, Kadry H, Lahooti B, Al-Obaida A, Ding Z et al. Pulmonary-arterial-hypertension (PAH)-on-a-chip: fabrication, validation, and application. Lab Chip. 2020;20(18):3334-45. https://doi.org/10.1039/d0lc00605j

38. National Institutes of Health – NIH. "Human-on-a-chip" models effects of opioid overdose. Washington: National Institutes of Health; 2020[acesso 5 set 2023]. Disponível em: https://heal.nih.gov/news/stories/Human-on-a-Chip.

39. Slaughter VL, Rumsey JW, Boone R, Malik D, Cai Y, Sriram NN et al. Validation of an adipose-liver man-on-a-chip model of NAFLD for preclinical therapeutic efficacy evaluation. Sci Rep. 2021;11:1-10. https://doi.org/10.1038/s41598-021-92264-2

40. Lam J, Lee B, Yu J, Kwee BJ, Kim Y, Kim J et al. A microphysiological system-based potency bioassay for the functional quality assessment of mesenchymal stromal cells targeting vasculogenesis. Biomaterials. 2022;290:1-16. https://doi.org/10.1016/j.biomaterials.2022.121826

41. Akhileshwar Jha L, Imran M, Shrestha J, Prasad Devkota H, Bhattacharya K, Alsayari A et al. Effectiveness of phytoconstituents and potential of phyto-nanomedicines combination to treat osteoarthritis. Eur Polymer J. 2024;215:1-22. https://doi.org/10.1016/j.eurpolymj.2024.113243

42. Dasari V, Bolimera P, Shukla S, Ganar R, Elwell T, Goyal R et al. Digital potency measurement: a new approach methodology for antisera effective dose assessments. Med Res Arch. 2023;11(12):1-11. https://doi.org/10.18103/mra.v11i12.4816

43. Punt A. New approach methodologies (NAMs) for human-relevant biokinetics predictions. Altex. 2020;37(4):607-22. https://doi.org/10.14573/altex.2003242

44. Mastrangeli M, Millet S, Mummery C, Loskill P, Braeken D, Eberle W et al. Organ-on-a-chip in development: Orchid final report. Leiden: Leiden University Medical Center; 2020[acesso 30 jan 2024]. Disponível em: https://h2020-orchid.eu/wp-content/uploads/2020/02/ORCHID-Summary.pdf

45. European Organ-on-Chip Society – EUROoCS. Home page. European Organ-on-Chip Society; 2024[acesso 30 jan 2024]. Disponível em: https://euroocs.eu/organ-on-chip/

46. National Institutes of Health – NIH. Tissue chip for drug screening. Washington: National Institutes of Health; 2024[acesso 28 ago 2023]. Disponível em: https://ncats.nih.gov/tissuechip

47. International Consortium for Innovation & Quality in Pharmaceutical Development – IQ. Home page. Washington: International Consortium for Innovation & Quality in Pharmaceutical Development; 2023[acesso 28 ago 2023]. Disponível em: https://iqconsortium.org/

48. Ingber DE. Human organs-on-chips for disease modelling, drug development and personalized medicine. Nat Rev Genet. 2022;23(8):467-91. https://doi.org/10.1038/s41576-022-00466-9

49. Stewart A, Denoyer D, Gao X, Toh YC. The FDA modernization act 2.0: bringing non-animals technologies to the regulatory table. Drug Discov Today. 2023;28(4). https://doi.org/10.1016/j.drudis.2023.103496

50. National Institutes of Health – NIH. Researchers create 3-d for rare neuromuscular disorders, setting stage for clinical trial. New Releases. 19 abr 2022[acesso 5 set 2023]. Disponível em: https://www.nih.gov/news-events/news-releases/researchers-create-3-d-model-rare-neuromuscular-disorders-setting-stage-clinical-trial

51. Mamani JB, Marinho BS, Rego GNA, Nucci MP, Alvieri F, Santos RS et al. Terapia de magneto-hipertermia no modelo de tumor de glioblastoma on-a-Chip. Einstein. 2020;18:1-8. https://doi.org/10.31744/einstein_journal/2020AO4954

52. Urbaczek AC, Leão PAGC, Souza FZR, Afonso A, Alberice JV, Cappelini LTD et al. Endothelial cell culture under perfusion on a polyester-toner microfluidic device. Scient Rep. 2017;7:1-12. https://doi.org/10.1038/s41598-017-11043-0

53. Ma HL, Urbaczek AC, Souza FZR, Leão PAGGC, Perussi JR, Carrilho E. Rapid fabrication of microfluidic devices for biological mimicking: a survey of materials and biocompatibility. Micromachines (Basel). 2021;12(3):1-13. https://doi.org/10.3390/mi12030346

54. Centro Nacional de Pesquisa em Energia e Materiais – CNPEM. LNBio importa tecnologia que substitui testes em animais por chips com células humanas. Portal MCTIC. 5 set 2016[acesso 29 jun 2023]. Disponível em: https://cnpem.br/lnbio-importa-tecnologia-que-substitui-testes-em-animais-por-chips-com-celulas-humanas/

55. Centro Nacional de Pesquisa em Energia e Materiais – CNPEM. Inédita na América Latina, tecnologia da Natura reproduz órgãos humanos em 3D para testes sem animais. CNPEM na Mídia. 28 mar 2023[acesso 29 jun 2023]. Disponível em: https://cnpem.br/inedita-na-america-latina-tecnologia-da-natura-reproduz-orgaos-humanos-em-3d-para-testes-sem-animais/

56. Rosalem GS, Torres LAG, Las Casas EB, Mathias FAS, Ruiz JC, Carvalho MGR. Microfluidics and organ-on-a-chip technologies: a systematic review of the methods used to mimic bone marrow. PLoS One. 2020;15(12):1-31. https://doi.org/10.1371/journal.pone.0243840

57. Presgrave O, Moura W, Caldeira C, Pereira E, Bôas MHV, Eskes C. Brazilian center for the validation of alternative methods (BraCVAM) and the process of validation in Brazil. Altern Lab Anim. 2016;44(1):85-90. https://doi.org/10.1177/026119291604400110

58. Agência Nacional de Vigilância Sanitária – Anvisa. Perguntas e respostas: métodos alternativos ao uso de animais e sua aceitação regulatória no âmbito de dispositivos médicos: webinar com a gerência de tecnologia de materiais de uso em saúde. Brasília: Agência Nacional de Vigilância Sanitária; 2022[acesso 28 ago 2023]. Disponível em: https://www.gov.br/anvisa/pt-br/assuntos/educacaoepesquisa/webinar/produtos/arquivos/p-r_webinar_metodos-alternativos_gemat_2022.pdf/view

59. Vulto P, Joore J. Adoption of organ-on-chip platforms by the pharmaceutical industry. Nature Rev Drug Discov. 2021;20:961-2. https://doi.org/10.1038/s41573-021-00323-0

60. Tagle DA, Morrison T, Walrath R. A regulatory perspective: how government funding spurs scientific innovation. Emulate Webinar. 18 jul 2023[acesso 18 jul 2023]. Disponível em: https://emulatebio.com/resources/a-regulatory-perspective-how-government-funding-spurs-scientific-innovation-on-demand-webinar/

61. Modor Intelligence. Organ on a chip market size & share analysis: growth trends & forecasts (2024 - 2029). Hyderabad: Modor Intelligence; 2024[acesso 5 fev 2024]. Disponível em: https://www.mordorintelligence.com/industry-reports/organs-on-chips-market

Acknowledgements

This work was carried out with the support of the Coordination for the Improvement of Higher Education Personnel - Brazil (CAPES) - Funding Code 001. The data is part of N.R.O.'s doctoral thesis in the Postgraduate Program in Health Surveillance at the National Institute for Quality Control in Health (INCQS). To the board of the Institute of Science and Technology in Biomodels (ICTB) for the opportunity to work on the project to implement OoC technology at the institute.

Authors' Contributions

Oliveira NR - Conception, planning (study design), data acquisition, analysis, and interpretation, and writing of the paper. Barroso WBG - Conception, data acquisition, and writing of the paper. Delgado IF - Conception and writing of the paper. All the authors approved the final version of the paper.

Conflict of Interest

The authors inform that there is no potential conflict of interest with peers and institutions, political or financial, in this study.