

Pradip Karale^a, Sakshi Ithape^d, Seema Gosavi^b, Nitin Sutar^c, Amit Narang^a, Agasti Ware^b, Nilesh Chaudhari^a, Anjali Gavit^d, Raosaheb Shendge^a

^aDepartment of Pharmaceutics, Sanjivani College of Pharmaceutical Education & Research (Autonomous), Savitribai Phule Pune University, Kopargaon, Maharashtra 423603, India

^bDepartment of Pharmaceutical Chemistry, Sanjivani College of Pharmaceutical Education & Research (Autonomous), Savitribai Phule Pune University, Kopargaon, Maharashtra 423603, India

^cDepartment of Pharmacognosy, Sanjivani College of Pharmaceutical Education & Research (Autonomous), Savitribai Phule Pune University, Kopargaon, Maharashtra 423603, India

^dDepartment of Pharmaceutical Regulatory Affairs, Sanjivani College of Pharmaceutical Education & Research (Autonomous), Savitribai Phule Pune University, Kopargaon, Maharashtra 423603, India

Corresponding author:

Mr. Pradip Karale

Assistant Professor, Sanjivani College of Pharmaceutical Education & Research, Kopargaon

Email- pradipkarale1@gmail.com

ORCID: 0009-0001-4086-2452

Received 20 Feb 2026; Received in revised form 24 Aug 2026 Accepted: 12 Oct, 2026; Available Online; 15 Oct 2026

ABSTRACT

The function of tissues and perhaps organs could be replicated utilize organ-on-a-chip technology. Clone organs, create functional organ-like components on a fluidic chip platform, and replicate the microbiome of humans. By getting rid of significant differences between cell cultures and common animal These bioengineered models have advanced toxicity testing & customized medicine. Organ chip technology may rebuild the human microbiota, recreate the physiology of tissues and organelles, and produce functional organs on multiple levels of chip substrates. The regulatory acceptance of OoC systems becomes even more important as they find applications into preclinical and clinical research spheres. Though dispersed, worldwide regulatory systems make standardisation and certification rather difficult. Along with the global regulatory landscape for OoC platforms, the legislative framework for OoC technologies in important countries namely the United States, the European Union, Japan, China, and developing nations is exhaustively examined in this review stressing the status, verification problems, and future orientations. The lack of uniformity, unclear classification, and reproducibility concerns create significant obstacles to regulatory approval. Forward-thinking initiatives like “Innovative Science and Technology Approaches for New Drugs” (ISTAND) Pilot project, which encourages the creation of pharmaceutical research contrivance have been started by the US Food and Drug Administration (FDA).

Keywords: Organ-on-Chip, Microphysiological Systems, Regulatory Science, Validation, FDA ISTDAND, OECD, EMA, Standardization

How to cite this article: Pradip Karale, Sakshi Ithape, Seema Gosavi, Nitin Sutar, Amit Narang, Agasti Ware, Nilesh Chaudhari, Anjali Gavit, Raosaheb Shendge, REGULATORY CHALLENGES AND VALIDATION PROTOCOLS FOR CHIP-BASED ORGAN MIMICRY, Int J Drug Deliv Technol. 2026;16(87s): 106-117; DOI: 10.25258/ijddt.16.87s.11

Source of support: Nil.

Conflict of interest: The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

1. Introduction:

Our way of knowing about and understanding human body systems has drastically changed from the use of microfluidic organ-on-chip device. These human organ mimicking devices have great potentiality in individualize medicine, ailment modeling and drug testing. offer phenomenal things on a small size.[1] With organ-on-a-chip technology, it is viable to use microfluidics to mimic experiments inside a living organ while still keeping the thousands of regulated variables seen in in vitro work. in vitro work is an important part of traditional cell work research and some opt to perform work in a test tube, on a culture plate or in some other setting outside of the live bodies. [2] The concept is expanded upon by organ-on-a-chip, which combines extracellular matrix (ECM) with microfluidic liquid control methods to grow cells and tissues, replicating the features of human organs on a

slide.[3] When it comes to developing novel medications, biomedical research has long relied heavily on animal testing. These differences often result in erroneous assessments of medication metabolism, efficacy, and toxicity, leading to therapies that are either ineffective or harmful, even if animal experiments have shown positive results.[4] Evidence indicates that more than 90% of drugs that get through animal tests don't work because of differences in body functions and how body uses the drug between animals and humans to make progress during human clinical trials.[5] While animal studies yield positive results, these discrepancies often result in incorrect estimates of drug metabolism, effectiveness, and toxicity, leading to treatments that are either ineffective or harmful.[6] OOC offer great benefits for medicine development, disease research and safety assessment compared with standard

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2D/3D cell culture systems.[7] The work of prime cells that can make progenitor cells in 3D tissue models shows a big step forward in our search for real alternatives to animal research. Since they better imitate the arrangement. Performance of body tissues, these models give a better base for testing toxicity and effectiveness.[5] A digital model of the ECM impacted by natural medium. It conserves the ECM's mechanical, biochemical, and geometrical attributes.[8] Its ability to rapidly generate intricate and random structures from digital designs makes it a prime candidate for creating medical devices, such as custom-made implants or surgical preparation models, tissue engineered scaffolds, drug delivery apparatus, and others.[9]

This development made it possible for research leading to revolutionary publications in the field. The Sasai laboratory created organoids derived from mESCs in the three-dimensional cerebral cortex in 2008; in 2009, intestinal organoids based on mouse ASC were developed. [10]

2. Overview of Organ-on-Chip Technology:

In organ-on-chip structure, the microfluidic chip is used to create biomimetic physiological organ systems that can replicate the organ's environment and forecast how it will react to stimuli.[11] Organ on a chip technology provide real micro environment for cell biology research by overcoming limitations of cell culture in vitro and allow toxicology and delivery of medication testing.[2,12]

OOC building typically follows its principles through the reductive analysis of the target organ.[13] The key advantage of employing an organ-on-a-chip approach is that it accelerates indagation;[14] because the devices are relatively cheap to make, equipment in house can be used to produce these chips (without the need for specialized tools) and so multiple remedies and portion can also be tested concomitantly. [15] Furthermore, a single-OOC platform that only uses one cell type may be used in conjunction with conventional culture media. Choosing the appropriate media for a single or multi-OOC platform with a variety of cell types, each with its own nutritional needs, is more difficult.[2]

findings are reliable and replicable across various organ-on-a-chip models

3. Working Principles-

3.1 Microfluidic Platform and Organ Culture-

The network of microscopic channels in microfluidic devices carries the nutrient, waste management and chemical gradient generation to mimic physiological environments. [16,17] Two separate media reservoirs are present on the outside platform, each with a unique hydrostatic head that fluctuates in pressure due to its location at the inlet. Two-way valves on the vessel offer outlets for programmable push/pull syringe pumps; if necessary, the system may be disassembled.[18] Using microfluidic devices, it is possible to mimic blood flow and tissue microenvironments in organic solvents (OOC), allowing for detailed management of fluid movement, nutrient supply, and waste disposal.[2] Single-cell omics has been studied in several animal cells, including the bulk of human cell types, using microfluidics. The study of cell morphology covers a broad spectrum of structural and exterior features, including their form, size, and surface texture.[19] A cyclic olefin copolymer (COC) was used to make a microfluidic chip, created for mass production, this material offers long-term durability, has the excellent optical characteristics for imaging, and has a low chemical absorption rate.[20,21]

3.2 Cellular Organization and Co-culture- Often divided by a porous membrane to simulate physiological barriers (e.g., alveolar-capillary barrier), primary human cells, iPS cell-derived cells, or specialised cell lines are seeded into the gadget. To simulate organ microenvironments, promote cell-cell interaction, and organ-specific function, more than one cell type (e.g., epithelial/endothelial) can be co-cultured. [21–23]

3.3 Integrated Sensing and Monitoring- Whether electrical, optical, or chemical, sensors that enable continuous monitoring of cellular condition, metabolic activity, and responses thereby reduce the demand for endpoint assays.[25] This platform was able to create integrated organ-on-chip models by combining different sensory systems with organ-on-chip models. This led to progress in drug testing. [25,26] There are several approaches to assess whether cells will grow adhesively or not (substrate dependence) during the design and production of this microfluidic platform. Adhesive cells' development and spread rely on the hydrophobicity of their substrate.[16]

3.4 Controlled Microenvironment and Ongoing Monitoring- Continuous perfusion of culture media via microchannels supports tissue viability by providing nutrients and removes pollutants. Dynamic, real-time observation of tissue responses, barrier integrity (e.g., TEER sensors), and cellular metabolism is made possible by inclusion of biosensors—electrical, optical, or biochemical. [27,28]

3.5 Biomimetic Mechanical Stimuli- OoC systems utilize mechanical loads in the form of cyclic stretching, compression, or flow-induced shear stress to mimic the physical microenvironment and biomechanical stimuli encountered in vivo (e.g., respire in lung-on-chip, peristalsis in gut-on-chip), essential to normal cell function and physiological response. [11,30]



Figure 1 strategies and factors to consider to ensure that the

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3.6 Modular and Multi-Organ Systems- The heart, liver, lungs, kidneys, and other organs may all be replicated using OOC technology. OOCs are all about small amount of liquid, safe stuffs, and sensors. The sensors can be one or more microsensors, an integrated output sensor, or an automatic imaging system.[2] Recent advances in bioengineering have enticed scientific interest in microfluidic-based tissue-on-a-chip systems, which are used to their full potential as small volume sensors.[31] Automation and high throughput are facilitated by multi-organ chips that support the management of cell culture, parallelism. To improve the reliability and similarity of experimental data, one needs a technology with reliable quality control and performance methods. [32,33]

4. Types of Organ-on-Chip Systems

Table 1 Organ-on-Chip Systems

Organ-on-Chip Type	Organs Modeled	Applications & Advantages	Ref .
Single-Organ Chip	Models individual organs (liver, heart, lung, kidney, intestine, skin)	The detailed cause of the disease, anatomy and function of organs examination, reliable diagnostic development, and effective and well tolerated therapeutic medications.	[34]
Multi-Organ/Body-on-a-Chip	A wide range of organ models are assembled on one platform	Multi-OoC systems are used to model complex diseases involving many organs, predict toxicity, and analyze the pharmacokinetics and pharmacodynamics of medications.	[35]
Organoid-on-a-Chip	Enhanced reproducibility, multi-organoid integration	Drug development, disease modeling, and other applications have made extensive use of OrgOCs.	[36,13]
Disease-Specific Chips	Establish to replicate specific conditions (e.g., rare genetic diseases, cancer, vascular problems)	Human related disease modeling, personalized medicine, Drug development	[37]

Sensor-Integrated Chips	Build biosensors to monitor in real time.	Improve data collection along with in-situ physiological signal analysis	[25, 38]
3D Bioprinted Chips	Making modified organ chips using in-situ monitoring sensors and 3D bioprinting technology.	It assists drug discovery by mimicking the body's conditions and the working features of real organs' functions and checking the therapeutic places on the chip in the lab of showing.	[3]

5.Organ-specific (OoC) Systems and Their Applications

Table 2 Organ-specific (OoC) Systems and Their Applications

OoC System Type	Applications	Ref.
Lung-on-a-chip	Disease stimulation (e.g., asthma, COPD), toxicity testing.	[39]
Liver-on-a-chip	Disease stimulation (e.g., hepatitis, fibrosis), hepatotoxicity testing, drug screening	[40,41]
Heart-on-a-chip	Screening of Cardiovascular agents, Cardiotoxicity testing, drug efficacy, modeling cardiac diseases	[42]
Kidney-on-a-chip	Drug modeling (kidney disorders), renal toxicity testing, and the creation of more effective drug discovery techniques.	[43]
Intestine-on-a-chip	Absorption studies, host-microbiome interactions, disease modeling using bioprinting technology to closely replicate the human small intestine. (e.g., IBD)	[44,45]
Skin-on-a-chip	Toxicology, wound healing, drug delivery studies	[34]

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Brain/Neural-on-a-chip	Neurotoxicity, neurodegenerative disease modelling (Alzheimer's disease), blood-brain barrier studies.	[46]
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6. Current Regulatory Framework for Organ on Chip

Standardization helps with data comparison across several investigations and businesses, hence supporting regulatory agency acceptance and permission for commercialization. Along with assessing platform data, it's imperative to make sure in vitro validation of tissue activity is strong, consistent, and reproducible. However, because there is no single approach or test that can be applied to all of these devices, the standardization and validation procedure is challenging. tissues produced using this method in vitro. [1] OOC technology improves cell culture approaches in order to produce more realistic human tissue settings, which results in better predictive biological culture models. [8,47]

6.1 International Standards for OoC-

The establishment of standards will involve several stages as this department is still in its introductory stages and not fully developed.[48] Standard Developing Organizations (SDOs) provide formal approval for standards, providing formalization of informal guidelines created by professional groups or consortia after consensus is reached. [49] Some of these are system standards: ISO/TC 210 (quality management and general aspects for medical devices), ISO/TC 276 (biotechnology), and CEN/TC 140 (in vitro diagnostic medical devices). Although they are not directly relevant to the OoC field, they provide a solid basis for spotting possible areas for development and major deficiencies. There might be some in the field. [50] The ISO/TC 48/WG 3 is currently working to standardise worldwide equipment. Named "Organ on Chip," the conference technical committee for Laboratory Equipment is ISO/TC 48. The microfluidic devices group is WG 3. [50,51]

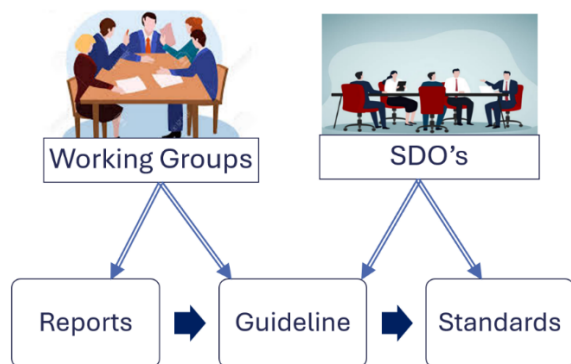


Figure 2 A demonstration of how standards are made and what working groups and standard development organizations (SDOs) do.

Using scientific evidence in standards will make it easier for stakeholders to accept, help the Master Production Schedule

sector grow, and create a market for kinder ways to test things without using animals. The Food and Drug Administration (FDA), the Medicine and Healthcare Products Control Board in Europe, and the European Medicines Agency have not yet officially classified organ-on-chip technology. Many companies that make organ-on-a-chip technology do not keep to any of the three rules: ISO 9001:2015, FDA 21 CFR Part 58, or FDA FD&C Act Section 507.[44]

6.1.1 The OECD

The organization for Economic co-operation & development (OECD) was begun in the year 1961, is a global organization Working with more than 100 countries, creating evidence-based standards.[53] This runs against the earlier edition, which is now included as Annex A in the OECD Series on Testing and Assessment No. 286, i.e. GIVIMP- "Guidance Document on Good In Vitro Method Practices." [54]

These guidelines handle essential assay aspects for validation, such as the rationale, approaches variability, endpoints and limitations, performance with reference and known compounds, and comparisons with established assays. Most importantly, the OECD rules also require that the data supporting the validity of the approach be available for review. [54,55]

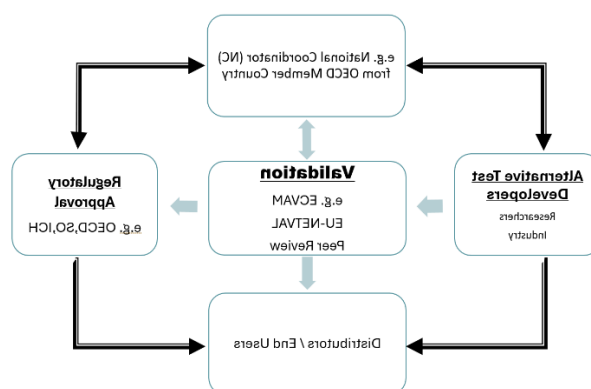


Figure 3 Illustration a regulatory approval & validation process for alternative test methods, within OECD framework

6.1.2 ISO/TC 48

ISO/TC 48/WG 3 aims for worldwide device standardization. ISO/TC 48 is the technical committee for laboratory apparatus; the working group is called "Microfluidic devices." The WG 3 is charged with setting a standard for the form of microfluidics, establishing a standard for microfluidics language (ISO 10991:2023), and setting a standard for Published recently is a standard for performance evaluation components and symbols for pumps (ISO/TS 6417); terminology of microfluidics (ISO 10991:2023) has been made available.[51,57]

6.2 USA

U.S. Centers for Medicare and Medicaid Service could be able to meet the CLIA requirements for clinical tests or precision therapy by using OoC models.[58] In the USA, Organ on Chip is under US Food and Drug Administration

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(FDA) supervision. FDA loves applied research as it teaches them what they do not know. If the European Organ-on-Chip Society and international groups specifically the NIH are to be the real winners, then they must participate in OoC systems to see that safe and effective products meet science and lawstan.[1]

6.2.1 FDA Modernization Act 2.0

The FDA Modernization Act 2.0 was progress on December 29, 2022. This extensive legislation permits the use of a variety of alternatives for sophisticated artificial intelligence (AI) methods, including language models and generative adversarial networks, among others. Animal testing, which employs cell-rooted analysis that contain human induced pluripotent stem cells (iPSCs), organoids, and organs on-chips (OoCs); and GANs.[57,59] One of the nonclinical experiments it described was “organic chips and microphysiological systems”.[60,61] The legislation is specifically modified to a “non-clinical test” done “in vitro”, “in silico”, or prior to or throughout the clinical study on animals. “in chemico” or a nonhuman “in vivo test” is a medication that has undergone a study phase to determine its safety and effectiveness.[62] The Act has led to awareness and funding for organ-on-chip research, especially in fields like tissue barrier models and liver, since these systems can better anticipate drug responses and provide more data that is useful to humans.[63]

6.2.2 FDA ISTAND Program

FDA has been more and more interested in using CIVMs to submit applications for IND, mainly in the field of modeling toxicity and disease. The FDA has shown an increased interest in utilizing IND applications for this purpose, even though they are not now supported by CIVMs. These models are needed because they are being used more to back up more traditional data. The FDA established the Innovative Science and Technology pilot program in 2020. The Innovative Strategies for New Drugs (ISTAND) program assesses cutting-edge scientific and technological strategies for new medications. Regulatory considerations drive the use of tools like Organ on Chips.[64]

6.2.3 FDA Alternative Methods Initiative- The FDA has come up with a new way of phasing away animal research for target therapies and other medicines and rely more on real-world human data. data using computers, Organoid testing and data.[65]

6.2.4 Qualification Programs

ISTAND Program: ISTAND introduces new technologies, including those that are more difficult to classify or have not been tested before, such as artificial intelligence or tissue chip analysis, to expand the range of measures that could be used to determine DDT eligibility and expedite approval pathways. [62,64,65]

Qualification for the Drug Development Tool (DDT): A letter of intent (LOI) outlining the drug evaluation resource, possible uses, and other information is required when submitting a DDT to the FDA and supporting data that demonstrates its suitability for the intended product before it can be included in a course that prepares you. The sender will put together an opening guidance package if the LOI is accepted. The structure for the presenter intended use of the

DDT is outlined in the briefing package.[68] The opening document should distinctly define and explain the intended contexts of use (COU) and describe how the DDT would improve medication development when compared to current methods.[69,70]

Medical Device Development Tools (MDDT)- The scientific basis of this tool makes it a useful resource for both device evaluation and regulatory decision-making.[71]

6.3 EU

6.3.1 Regulatory Agency- European Medicines Agency (EMA)

The "Three Rs (3R) principle, i.e. replacement, reduction, refinement" paradigm, which served as the basis for William Russell and Rex's EMA 3Rs Principle, is based on it The EU has mandated that the Burch 1958 under the EMA 3Rs Principle and the book The standards of Humane Experimental Technique adhere to articles 4 and 13 of Directive 2010/63/EU. The Burch 1958 by the EMA 3Rs Principle and The Principles of Humane Experimental Technique book were required to follow articles 4 and 13 of Directive 2010/63/EU by the EU. The recent PSIS (Putting Science into Standards) workshop, which was held with the support of the Cosmetics Regulation 1223/2009 and REACH-the registration, evaluation, approval, and restriction of chemicals, was also. The European Committee for Electrotechnical Standardization and the European Committee for Standardization are both based in Europe. [72,73] The Joint Research Centre and the European Committee for Electrotechnical Standardization, with the support of the European Committee for Standardization, have proposed that: within the OoC plan standard development process, EUROoCS is the contact point.[74]

CEN/CENELEC Standardization- The European codification Organizations CEN and CENELEC (CEN-CNLC) conduct regular surveys of standardization efforts under the auspices of the European Commission's Joint Research With which they work is center. The project is titled "Putting Science into Standards" (PSIS). The 2021 PSIS workshop will cover OoC.[49,75] One of the aims of harmonising the procedures from one European state to the other and reaching the international standards set up among the world community especially those by OECD, means the standardization of device materials, interfaces, biological tests and data management.[74] ECVAM stands for the European's disposable center for the validation of alternative methods, which aims at promoting and validating new methods of tests.[76]

6.3.2 European Union Framework

European Organ-on-Chip Society (EUROoCS): The European Organ-on-Chip Society (EUROoCS), set up by ORCHID, aims to foster and promote the continuous progress of OoC networks. To encourage and support OoC research as well as to support chance for knowledge and skill sharing and development in this area in order to enhance everyone's health is its goal. [75,76]

ORCHID Vision session: Standardizing this OoCs is challenging. Many programs have acknowledged the need of standardization in order to advance the field, as have important players in the OoC industry, and have advocated

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for legal approval and certification. The Organ-on-Chip In Development (ORCHID) project hosted a standards strategy workshop in 2019 to generate a viewpoint and recommendations by gathering developers of OoCs, end-users, and regulators.[79] Leiden University Medical Center is the center for the European Commission ERIC project ORCHID as some part of the Dutch Organ-on-Chip Consortium, hDMT. Grantees of this project, awarded under grant no. 766884 by the European Parliament research and innovation program. The two-year, 2017–2019 effort sought to develop an organ chip research program and a stakeholder network. [80–82] Focusing on prerequisite, or performance of the OoCs preferably than verification is very crucial.

In 2017, the Ministry of Economy, Trade, and Industry helped the Japan Agency for Medical Research and Development (AMED) in the AMED-MPS project. [83,84]

6.4 India

The Centre for Predictive Human Model Systems (CPHMS), a science and policy centre in India, is committed to scientific progress through the use of scheme that are closely resembling those found in the Human body. It was created as a joint venture among Atal Incubation Centre (AIC-CCMB) and Humane Society International (HSI)-India.[85–87] Although no form of legislation is presently in place that specifically refers to OoC; the Central Drugs Standard Control Organization (CDSCO) refers to wearable devices that are used for temperature monitoring in non-patient settings and, thus, categorizes these devices as PETs.

6.5 Other Major Jurisdictions

6.5.1 Japan (PMDA)

The standardisation of cells has been a major area of interest for Japan, with ISO/TC 276 Biotechnology being endorsed as the primary standard. ISO/TC276/WG2 aims to coordinate and align the offerings of members of the different biobanking community so they may modify their own set of tools to suit their specific demands. All biobanks will be able to make the most of the resources available to them if they have both standards and best practices that complement each other. New biotechnology breakthroughs and a brighter future will be facilitated by more complementary standards, tools, and best practices. [86,87]

6.5.2 Health Canada

The use of genetic therapy and biotherapy are included in the biological therapies detailed in the Food and Drugs Act, which is controlled by Health Canada. If a product is used similarly to others and needs only minor changes, still the Regulation on the well-being of Human Transplantable Cells, Tissues, and Organs (CTOR) might detain authority over such a product. [88,89] In 2007, a new class of cells, tissues and organs (CTO) for transplant was approved for use as CTO therapy. CTO therapy, class of RNA in the class of cells that are minimally modified and tissues, as well as organs, mechanisms similar to those already in use can be, from the time of, homologous transplant.[92]

6.5.3 Brazil

The non-profit research institute attached to a school of higher learning, the Center for Research and Advancement of Fragments and Molecular Targets (CRAFT), works to find

new ways to attack diseases the WHO has named as ones we do not pay enough attention to, such as leishmaniasis, Chagas, schistosomiasis. It uses something new that mixes the old art of finding drug candidates based on small compound pieces with new ways of peering into the shapes of targets and testing for way compounds link with them.[93]

6.5.4 Asia-Pacific- (China, Singapore, South Korea, Taiwan)

The Asia-Pacific region (including nations like Taiwan, South Korea, China, and Singapore) has been designated as the emerging market as a result of government promotion of healthcare technologies. For example, the five-year initiative dubbed "Organ Reconstruction and Manufacturing" was launched by the Chinese Academy of Science in 2018. As funding continues to increase, the technologies are anticipated to improve and become more affordable. Products made by Organ-on-a-Chip will be embraced by the pharmaceutical industry, and demand for them is predicted to rise significantly. [94,95]

7. Future challenges

The insufficiency of international standards: There is no global standard for the design, qualification, or performance of organ-on-chip devices. Standardization is essential for repeatability, device compatibility, and regulatory clearance, but the field's variety and pace of change make it difficult to harmonize protocols and evaluation methods.[96]

High cost: OoC device are not readily accessible due to intense functional and development charge, which also necessitate the use of advanced sensors. Their broad adoption in both industry and education is hampered by the economic constraint. [11,97] OOAC technologies have made significant progress, but the pace of advancements and widespread utilization in drug invention remains prolonged.[58]

Engineering and Technical Challenges: Popular material for organ-on-chip applications, polydimethylsiloxane (PDMS) is affordable and easy to manufacture. It has several disadvantages, including optical interference in some assays, oligomer leaching of uncrosslinked material, adsorption of hydrophobic compounds, and a shallow channel height of around 200 μm . [98,99] In response to these limitations, scientists have explored substitute materials in the hopes of finding means to enhance the user-friendliness and reliability of microfluidic devices.

Challenges in getting cells: Although primary cells may spend all their lives doing everything in vivo, they are rarely used due to the fact that it takes time to grow phenotypic changes as well as in vitro replication of primary cells. They are extensively used in OOACs. [37,42] A significant objective is to produce goods that can be scaled up and used in clinical laboratories in a way that is both reproducible and long-lasting.[100] The creation of chips with a biological condition that can be tested and the collection of patient tissue samples (organoids) and iPSCs are further problems. To make useful diagnostic or prognostic testing devices for clinical decisions, chips must be prepared for experimentation within days after seeding process.

Other Challenges:

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Multi-disciplinary issue needing to be addressed is the difficulty of linking several organ systems. These systems have several drawbacks in addition to limited volumes or oscillating drug levels for biologically relevant measures: poor mixing capacity between organs, a lack of meticulously controlled sampling between links, and the rigidity of the organ connection order.[101]

Microfabrication plants might or might not employ the same quality control procedures as those used in cell culture. The demand for design organs-on-a-chip may increase as industry and commerce progress. [101,102]

Even though microdevices have many benefits over older models such as being cheap, safer, flexible and capable of doing many things at once, the immune system is still a very important thing, but it has its limits like the mesangial cells which are absent. [104,105]

8. Summary

The new micro physiological system called organ-on-chip (OoC) amplifies human organ operational on a tiny scale and contain great assurance for drug development. drug testing, disease studying, and product making. This new technology fixes many problems with old tools and cuts down on animal tests. It delivers data that is more accurate and more like what will happen in living humans.

8.1 Current Regulatory Framework

United States (FDA): Among other routes for OoC acceptance defined by the FDA are ISTAND and the FDA Modernization Act 2.0; the FDA recently certified the Emulate Liver-Chip for Analysis of drug-induced liver damage. European Medicines Agency (EMA): The European Medicines Agency (EMA) focuses on 3Rs principles, early scientific advice and the coordination of member states policies.

International Standards: OECD and ICH are adding OoC into test recommendations; ISO and CEN-CENELEC are driving standardizing in terminology, materials, and validation methods.

8.2 Challenges

Lack of international standards: Protocol harmonization is hampered by diversity and rapid innovation, and OoC devices lack any global design, qualification, or performance criteria. High cost: Expensive development, maintenance, and demand for sophisticated sensors restrict industrial and educational adoption via high-cost barrier.

Cell sourcing challenges: Cell sourcing challenges Scarce, phenotypically altered over time, and difficult to duplicate in vitro are primary cells.

Material limitations: Though simple to use, PDMS has shortcomings including optical interference, oligomer leaching, hydrophobic molecule absorption, and shallow channels (~200 µm); other materials are under investigation.

9. Conclusion

Organ-on-chip technology is at the crossroads of regulatory science and pharmaceutical R&D. Actively promoting its use, the main regulatory agencies such as FDA and EMA have led the way to global acceptance. A standardized platform for terminology, performance verification, and data submission is being established through ISO, CEN-

CENELEC, and OECD's international standardization. For the most part accepted, the following are vital:

Harmonization of demand and validation needs prevents geographic division.

Technical regulation: uniform data format, equipment design, and cell sourcing procedures.

To gain confidence in predictive capability, inter-laboratory validation tests at scale are used.

Regular cooperation among CROs, academics, industry, and authorities form a collaborative ecosystem.

Better reliability and scalability are achieved via integration of emerging technologies like artificial intelligence, sophisticated manufacturing, and sensor systems.

Over the next three to five years, stakeholder cooperation and regulatory innovation will determine whether organ-on-chip technology develops from a fascinating niche technology into an accepted mainstream device in drug development, thereby improving patient protection, expediting drug approvals, and realizing the vision of substantially replacing animal testing.

Funding statement

Nil.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Acknowledgment

All authors express gratitude to the organization of SRES, Sanjivani College of Pharmaceutical Education & Research (Autonomous), Kopergaon, India, for providing the necessary facilities for the completion of this research work.

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