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Report to Congressional Addressees

May 2025

TECHNOLOGY ASSESSMENT

Accessible Version

Human Organ-on-a-Chip

Technologies Offer Benefits Over Animal Testing but Challenges Limit Wider Adoption

GAO-25-107335

The cover image displays a stylized representation of an organ-on-a-chip.

Cover source: GAO analysis of scientific literature (data and illustration); Paul/Bidala/Kwangmoozaa/Kuz Production/Шамиль Алиев/Pakhnyushchyy/Инна Харламова/stock.adobe.com (images). | GAO-25-107335

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Highlights of GAO-25-107335, a report to congressional addressees

May 2025

Why GAO did this study

Biomedical researchers face challenges investigating human biology, disease, and the body's responses to external chemicals, including medicines. Conventional methods—such as animal testing and cells in a petri dish—often do not translate into similar results for humans because they cannot effectively replicate the complex systems of the human body. In the past decade, however, researchers in the pharmaceutical, chemical, and biodefense industries have begun developing and using OOCs to help improve our understanding of human disease and responses to drugs and other chemicals.

This technology assessment examines (1) current and emerging OOC technologies and their potential benefits, (2) challenges to developing and using these technologies, and (3) options that policymakers could consider to help enhance the benefits or mitigate the challenges.

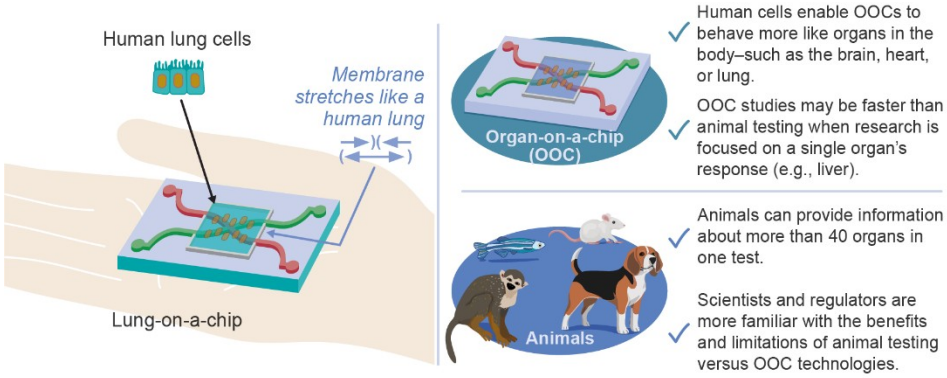
To conduct this work, GAO reviewed scientific literature and federal agency documents; interviewed a range of experts from government, industry, academia, and nonprofit organizations; and convened a discussion group of 16 experts. Participants included federal agency officials, policy experts, and OOC developers and end users from industry and academia. GAO is identifying policy options in this report (see next page).

View GAO-25-107335. For more information, contact Karen L. Howard, PhD, at HowardK@gao.gov.

What GAO found

Human organ-on-a-chip (OOC) is an emerging technology that incorporates human adult cells in a small laboratory device to mimic how organs work—such as the brain, heart, or lungs. OOCs may be designed to simulate the mechanics of human organs, such as a lung-on-a-chip that stretches to simulate breathing. Researchers are developing and using OOCs to model diseases and predict responses to chemicals. For example, companies are using OOCs to assess aspects of drug safety and efficacy. Because OOCs contain human cells, their use in research may have more relevance to humans than animal testing or other conventional lab methods, but certain OOC research may cost more and take longer. Currently, OOCs cannot replace animal testing but may be used alongside animals. The next generation of OOC is focused on developing "body-on-a-chip" systems that link together multiple OOCs—such as the intestine, liver, and kidney—to investigate how organs interact.

Lung-on-a-chip (left) and how organ-on-a-chip compares to animals (right)



Source: GAO analysis of scientific literature (data); U.S. Food and Drug Administration image licensed via BioRender.com as modified by GAO, Greenvector/Инна Харламова/Happypictures/Creativestore/Marina/wordspotrayal/stock.adobe.com (images). | GAO-25-107335

GAO identified several challenges to the development and use of OOCs, including

Obtaining human cells. Reliable human cells are a key requirement for using OOCs, but availability is limited. For example, experts told GAO that only 10 percent to 20 percent of human cells they purchase are high enough quality for OOC studies.

Lack of benchmarks and validation studies. The lack of benchmarks and sufficient studies assessing OOC accuracy, reliability, and relevance hinders the ability of end users, such as drug companies, to understand how OOCs compare to conventional methods, including animals, and data from clinical trials.

Limited data sharing. OOC developers and end users may be reluctant or lack capacity to share their OOC research findings. For example, companies may be concerned about intellectual property and loss of competitive advantages.

Regulatory uncertainties. Regulators are still working to better understand OOCs. Meanwhile, experts told GAO that the OOC field faces regulatory uncertainties, including regulators' lower level of familiarity with OOCs than other methods, and unclear guidance and messaging from the U.S. Food and Drug Administration.

GAO developed six policy options that could help mitigate challenges to OOC development and use, including the option to maintain the status quo. The options identify possible actions by policymakers, including legislative bodies, government entities, academia, industry, and other groups. See tables 1–6 in this report for additional policy options and details.

Selected Policy Options to Help Mitigate Challenges to the Development and Use of Organ-on-a-Chip (OOC) Technologies

Selected policy option	Opportunities	Considerations
Support efforts to increase access to diverse, high-quality human cells (report p. 25) *For example, federal entities, together with stakeholders from academia and industry, could support the establishment of high-quality cell banks and biospecimen repositories that incorporate population diversity.*	• Could provide OOC developers and end users with a supply of diverse human cells for future OOC research. • Current efforts to establish cell banks for related technologies may provide a model for these efforts.	• May require a high level of stakeholder coordination, additional resources, and scientific expertise. • May require additional standardized cell protocols and reference materials.
Encourage more research and development of benchmarks and validation studies (report p. 27) *For example, relevant funding agencies could provide more funding to academics and companies for OOC research, specifically to validate OOCs for priority contexts of use.*	• Could help to identify relevant benchmarks to validate OOCs for specific contexts of use. • Could increase the number of published validation studies. • Could increase scientific confidence in OOCs.	• Investments in OOCs may reduce available funding for other technologies. • Defining priority contexts of use will require input from and coordination with end users, such as drug or chemical companies.
Create or participate in mechanisms for data sharing (report p. 28) *For example, OOC developers and drug companies could participate in precompetitive efforts to share OOC data freely, such as sharing data through an industry trade group, nonprofit, or other trusted third party.*	• Could help end users and regulators assess the robustness of OOC. • Could build confidence in and aid adoption of OOC. • Could increase alignment and engagement among relevant stakeholders.	• Companies may need additional incentives to participate for fear of losing a competitive advantage. • May require an assessment of which OOC methods would be most likely to benefit.
Provide additional regulatory guidance (report p. 29) *For example, regulators could provide detailed guidance on how specific OOCs could more readily replace a conventional laboratory method.*	• Clarity from regulators on appropriate use cases within their regulatory purview could build confidence in the models and increase regulatory experience with these data.	• This approach may not be helpful for certain OOC use cases. • Could require regulatory agencies to dedicate resources to these new efforts. • Guidance that is too specific could constrain developers and end users.

Source: GAO. | GAO-25-107335

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Abbreviations

Abbreviation	Word or phrase
3D	three-dimensional
DARPA	Defense Advanced Research Projects Agency
DOD	Department of Defense
EPA	Environmental Protection Agency
FDA	U.S. Food and Drug Administration
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
ISO	International Organization for Standardization
ISTAND	FDA's Innovative Science and Technology Approaches for New Drugs Pilot Program
NCATS	National Center for Advancing Translational Sciences
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
OOC	organ-on-a-chip
OECD	Organisation for Economic Co-operation and Development
TEX-VAL	Texas A&M Tissue Chip Validation Consortium

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May 21, 2025

The Honorable Bill Cassidy, M.D.
Chairman
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Rand Paul, M.D.
Chairman
Committee on Homeland Security and Governmental Affairs United States Senate
The Honorable Zoe Lofgren
Ranking Member
Committee on Science, Space, and Technology
House of Representatives

Biomedical researchers face challenges investigating human biology, disease, and the body's responses to external chemicals. For example, drug developers spend an average of 6 years testing a new drug candidate for potential safety and efficacy using animals, simple cell cultures, and other conventional laboratory methods before moving into human clinical trials.[1] However, up to 80 percent of drug candidates that show promise at this stage still fail to display sufficient safety and efficacy in humans to achieve regulatory approval. One reason that conventional methods may not translate into similar results for humans is that the methods often do not effectively replicate how the complex systems of the human body work. Meanwhile, U.S. researchers use millions of animals for research each year, sometimes using procedures that cause animals pain or distress.

In recent years, researchers have shown that human organ-on-a-chip (OOC) technologies can mimic the structures and functions of human organs, model diseases, and predict responses to chemicals. For example, drug and chemical company researchers have begun using OOCs to assess the potential safety or efficacy of products under development. The U.S. Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) have also begun using some OOC data to make determinations about the safety or efficacy of drugs and other chemicals.

For decades, Congress has directed federal agencies to identify replacements for animals in safety and efficacy testing when scientifically justified. For example, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Authorization Act

[1]For the purposes of this report, conventional laboratory methods include testing on animals—such as mice, rats, fish, dogs, and nonhuman primates (e.g., monkeys)—and simple cell-based methods—such as human cell cultures.

of 2000, established ICCVAM as a permanent interagency coordinating committee and directs it to, among other things, evaluate alternatives to animal testing for regulatory uses.[2] ICCVAM is composed of officials from federal regulatory agencies (FDA and EPA) and research agencies, including the National Institutes of Health (NIH).[3] In March 2024, ICCVAM released a report that describes how developers and end users can build more confidence in technologies such as OOCs.[4] The Toxic Substances Control Act, as amended in 2016, directs EPA to reduce and replace vertebrate animals in the testing of chemical substances or mixtures, to the extent practicable, scientifically justified, and consistent with the Toxic Substances Control Act.[5] The Food and Drug Omnibus Reform Act of 2022 amended the Federal Food, Drug, and Cosmetic Act to add the term "nonclinical test," which clarifies that drug application sponsors can submit results from alternative methods to animal testing to support investigational new drug applications.[6]

GAO has completed prior work on the potential use of OOCs in biomedical research, including for vaccine development and as alternatives to animal testing.[7] In light of congressional interest in alternatives to animal testing, we prepared this report under the authority of the Comptroller General to further assess OOCs.[8] This report examines: (1) current and emerging OOC technologies and their potential benefits, (2) challenges to developing and using these technologies, and (3) options that policymakers could consider to help enhance the benefits or mitigate the challenges.

To address these objectives, we conducted a literature search; interviewed experts from government, industry, academia, and nonprofit sectors; convened a 2-day expert discussion group; and visited labs researching OOCs at the National Institute of Standards and Technology

[2]Pub. L. No. 105-545, §3, 114 Stat. 2721, 2721-23 (codified at 42 U.S.C. §285l-3). ICCVAM is a permanent interagency coordinating committee of the National Institute of Environmental Health Sciences, which is an institute within the National Institutes of Health. ICCVAM can, in an advisory capacity, establish opportunities for research collaboration, including between federal regulatory agencies and research laboratories.

[3]The Act specifies that ICCVAM be composed of the heads (or their designees) of 15 agencies or subagencies, also including the Department of Defense (DOD), and any other agency "that develops, or employs tests or test data using animals, or regulates on the basis of the use of animals in toxicity testing." Pub. L. No. 105-545, §3(c), 114 Stat. 2721, 2722 (codified at 42 U.S.C. §285l-3(c)). The National Institute of Standards and Technology (NIST) joined voluntarily in 2016. The National Center for Advancing Translational Sciences (NCATS) joined in 2024. DOD's Defense Threat Reduction Agency told us that it has initiated conversations to become full members before the next technology meeting in spring of 2025.

[4]ICCVAM, *Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies* (March 2024).

[5]Pub. L. No. 114-182, tit. I, § 4, 130 Stat. 448, 452-454 (2016) (codified at 15 U.S.C. 2603(h)). The Toxic Substances Control Act, as amended, directs EPA to assess and regulate risks from new chemicals prior to manufacturing and existing chemical substances in commerce. Pub. L. No. 94-469, 90 Stat. 2003 (1976) (codified, as amended, at 15 U.S.C. § 2601 et seq.).

[6]Pub. L. No. 117-328, tit. III, subt. B, ch. 1, § 3209, 136 Stat. 4459, 5821-22. The Food and Drug Omnibus Reform Act of 2022 was enacted as part of the Consolidated Appropriations Act, 2023.

[7]GAO, *Vaccine Development: Capabilities and Challenges for Addressing Infectious Diseases*, GAO-22-104371 (Washington, D.C.: Nov. 16, 2021); GAO, *Animal Use in Research: Federal Agencies Should Assess and Report on Their Efforts to Develop and Promote Alternatives*, GAO-19-629 (Washington, D.C.: Sep. 24, 2019).

[8]31 U.S.C. § 717(b)(1).

(NIST) to better understand these technologies. See appendix I for the full objectives, scope, and methodology used in this report and appendix II for the list of experts we spoke with.

We conducted our work from January 2024 through May 2025 in accordance with all sections of GAO's Quality Assurance Framework that are relevant to technology assessments. The framework requires that we plan and perform the engagement to obtain sufficient and appropriate evidence to meet our stated objectives and to discuss any limitations to our work. We believe that the information and data obtained, and the analysis conducted, provide a reasonable basis for the findings and conclusions in this product.

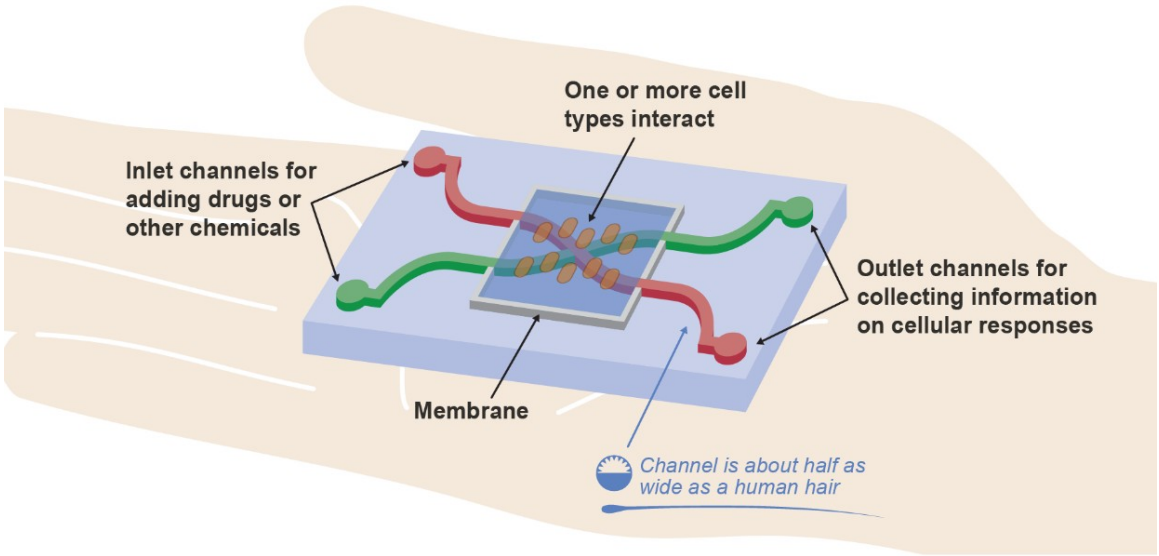
1 Background

The human body includes about 80 organs—such as the brain, lungs, heart, liver, and more—made up of at least 200 distinct cell types that perform special, critical functions. Blood delivers oxygen and nutrients to cells within these organs and removes waste products. Various stakeholders, including companies and academic labs, are developing OOCs that attempt to effectively mimic the complexity of these organs in laboratory settings to investigate human biology.

1.1 OOCs can model the structure and functions of human organs

While there is no consensus definition, we defined OOCs in our previous reporting as small, experimental laboratory tools that contain human cells and mimic how organs and systems work in the human body.[9] For example, OOCs may contain multiple cell types with media—a liquid that provides nutrients to support cell function—flowing through small channels in a three-dimensional (3D) system that mimics blood moving through an organ (see fig. 1).

Figure 1: The general design of a human organ-on-a-chip



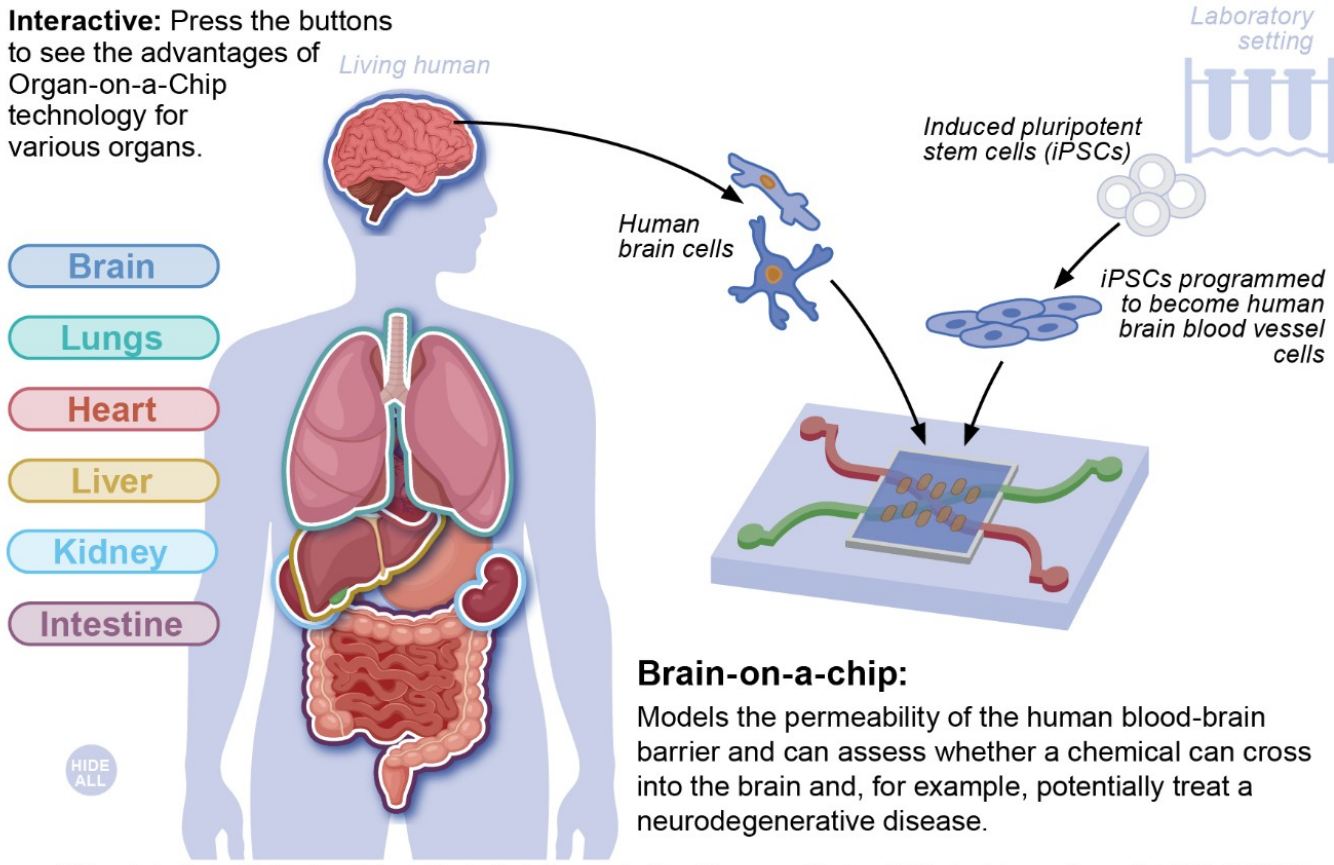
Source: GAO analysis of scientific literature (data); U.S. Food and Drug Administration image licensed via BioRender.com as modified by GAO (image). | GAO-25-107335

[9]Some definitions of OOCs include other cell-based laboratory tools referred to as complex *in vitro* models or microphysiological systems. These include organoids—small, artificially grown groups of human cells that resemble an organ and mimic the original tissue architecture—which we include in our definition of OOC for this report. For a previous report where we described OOCs, see GAO, *Vaccine Development: Capabilities and Challenges for Addressing Infectious Diseases*, GAO-22-104371 (Washington, D.C.: Nov. 16, 2021).

1.2 Types of OOCs include brain-on-a-chip, heart-on-a-chip, liver-on-a-chip, and more

OOCs can model structures and functions of various human organs (see fig. 2). OOCs may be designed to simulate the mechanics of human organs, such as a lung-on-a-chip that stretches to simulate breathing. These technologies may also integrate sensors that conduct real-time measurements of cellular responses, such as a heart-on-a-chip that contains an electrochemical sensor to assess heart function.

Figure 2: Examples of human organ-on-a-chip technologies and uses



Source: GAO analysis of scientific literature (data and illustration); Greenvector/Инна Харламова/ Eveleen007/stock.adobe.com (images). | GAO-25-107337

1.3 Other laboratory methods help scientists investigate how the human body works

Besides OOCs, biomedical researchers use the following conventional methods to gain insights about human biology, disease, and responses to external chemicals, including industrial chemicals and drugs.

Simple cell-based methods. In contrast to OOCs, other cell-based methods (e.g., human cell cultures) primarily involve cells of a single type sitting on a flat plastic surface—such as a

petri dish—with media on top of them. Researchers use these methods to provide low-cost, rapid answers to biomedical research questions, including possible organ toxicity from an industrial chemical (e.g., a pesticide) and early indications of drug efficacy. However, simple cell-based methods lack the ability to mimic many structural and functional characteristics of organs in the body—such as continuous flowing media and mechanical simulations—that may affect their ability to predict responses in people. Because they lack these physiological characteristics, they are less complex than OOCs.

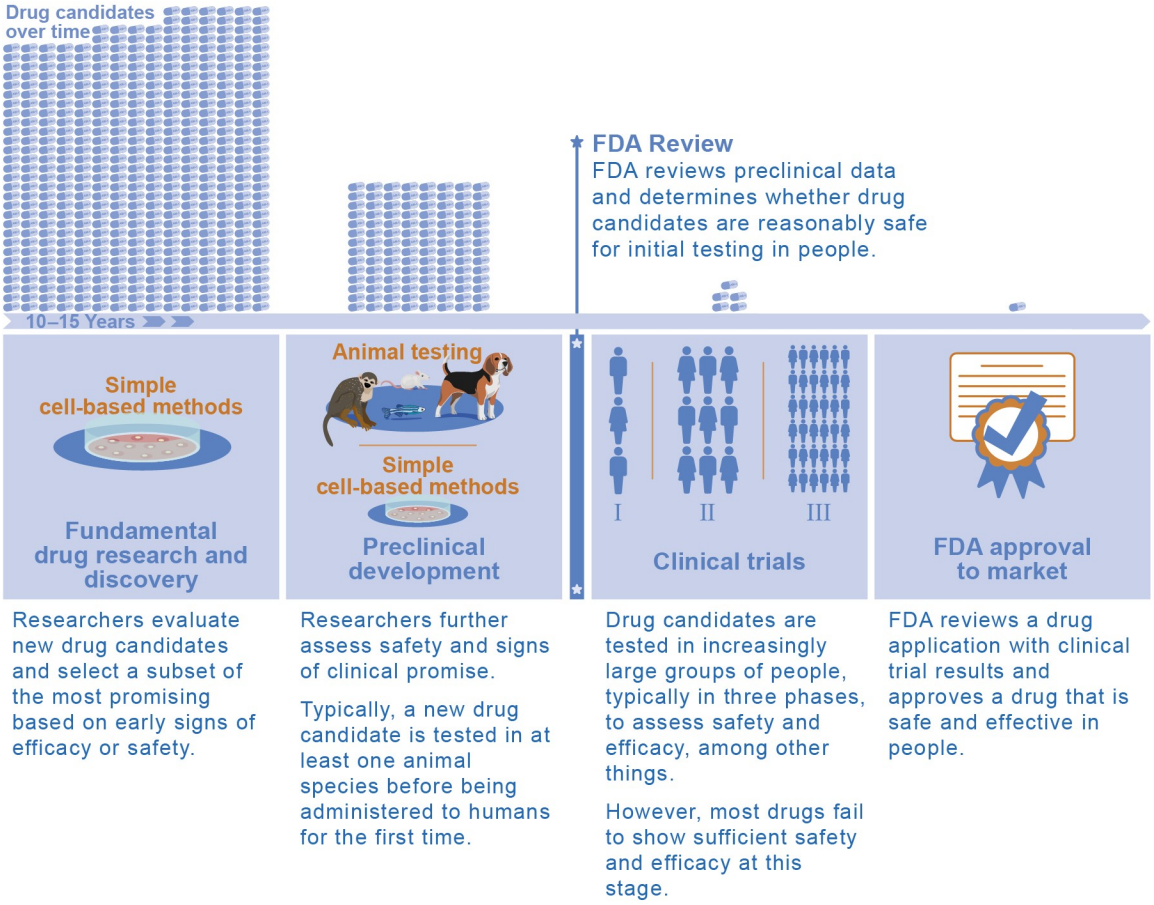
Animal testing. Animals—such as mice, rats, fish, dogs, and nonhuman primates (e.g., monkeys)—are used to better understand human biology, test the potential safety of chemicals, and test potential safety and efficacy of drug candidates before they are tested in people.[10] Animals can provide whole-organism information on more than 40 organs and tissues in a single experiment. For example, biomedical researchers might study the side effects of a drug candidate on "off-target" organs, such as an animal's gallbladder. While animal testing has led to treatments and cures for many human diseases, we previously reported that most animal research does not result in an approved drug or treatment that would benefit human health due, in part, to inherent biological differences between animals and humans.[11] For example, the lack of effective treatments for Alzheimer's disease, asthma, and other disorders is due, in part, to the reliance on genetically engineered mice that do not accurately mimic human diseases. In addition, animal testing can cause pain and distress to animals and presents other ethical issues for stakeholders and the public.

Biomedical researchers may choose which methods to use based on the current scientific evidence, their needs, and available resources. For example, drug developers may use simple cell-based methods and animals to assess potential safety and efficacy for multiple drug candidates before selecting candidates to test in clinical trials (see fig. 3).

[10]Nonhuman primates represent a very small percentage of the animals used in research, according to an expert and reported estimates.

[11]GAO, *National Institutes of Health: Assessing Efforts to Improve Animal Research Could Lead to Greater Human Health Benefits*, GAO-25-107140 (Washington, D.C.: Dec. 19, 2024).

Figure 3: The general steps and common time frame for drug development



Source: GAO analysis of information from the U.S. Food and Drug Administration (data); GAO (icons); Greenvector/Happypictures/Creativestore/Marina/wordspotrayal/stock.adobe.com (images). | GAO-25-107335

Note: The steps and time frames for drug development depicted in this figure are not drawn to scale. Development steps and time frames for a specific drug may vary.

1.4 Various stakeholders are working on OOCs

Stakeholders across multiple sectors—including government, industry, and academia—are involved with OOC development, use, regulation, and coordinating activities. These groups include

Developers. These stakeholders create or market OOCs as a product or service. Companies, universities, and government labs are involved in OOC development and have published articles in peer-reviewed journals about proof-of-concept OOCs that may or may not be commercial. Some companies are developing commercially available OOC systems that require proprietary supporting equipment, while others are developing OOCs that readily adapt to existing lab infrastructure. In addition to selling the systems, another business model is to perform OOC experiments for clients as a contract research organization.

End users. Government, industry, and academic labs use OOCs to investigate

fundamental aspects of human biology, disease, and responses to chemicals. Government and academic researchers may use OOCs in basic research to discover mechanisms of human disease or to support toxicological assessments. In addition, drug companies may use OOCs for disease modeling and in many aspects of drug development, including safety and efficacy assessments of new drug candidates and therapies.

Regulators. FDA and EPA review OOC data from companies regarding safety, efficacy, or OOC performance. FDA may review OOC data in drug development and regulatory reviews—for example, before a new drug candidate is moved into clinical trials. EPA may review OOC data from companies supporting various aspects of chemical safety as part of its risk assessment of new chemical substances.[12] FDA and EPA also support or conduct research related to OOCs.

Coordinating bodies. These stakeholders include trade groups, public-private partnerships, standards organizations, and government interagency committees. Groups such as these coordinate and conduct research on OOCs and related technologies. Relevant public-private partnerships include the Critical Path Institute, which hosted FDA-funded OOC workshops in 2023 and 2024 that included companies, academics, FDA staff, and others. NIST hosted an OOC standardization workshop in 2023 that included FDA, NIH, and OOC developers.

In addition to ICCVAM, NIH has started other recent interagency efforts. In 2024, the NIH Office of Strategic Coordination (specifically the NIH Common Fund) launched the Complement Animal Research In Experimentation program—referred to as Complement-ARIE—with the goal of accelerating research approaches that more accurately model human biology.[13] Also in 2024, NIH's National Center for Advancing Translational Sciences (NCATS), in partnership with FDA, established four university-led Translational Centers for Microphysiological Systems (TraCe MPS) with the goal of qualifying OOCs as drug development tools through FDA.[14] In April 2025, NIH announced plans to establish the Office of Research Innovation, Validation, and Application within NIH's Office of the Director, which will coordinate NIH-wide efforts to develop, validate, and scale the use of non-animal approaches, among other things.[15]

[12]EPA's Office of Chemical Safety and Pollution Prevention reviews OOC data. This office includes the Office of Pesticide Programs, which regulates the manufacture and use of all pesticides in the U.S., and the Office of Pollution Prevention and Toxics, which evaluates new and existing chemicals and their risks, as well as performing other functions. For new chemical substances (i.e., substances that are not already listed on the Toxic Substances Control Act [TSCA] inventory), or a significant new use of an existing chemical substance, TSCA Section 5(a)(1) requires that a person submit to EPA a notice at least 90 days before commencing manufacture of a new or significant new use of a chemical substance and directs EPA to determine the risk of injury to health or the environment of the chemical and takes any subsequent required actions to mitigate the risk after such a determination. 15 U.S.C. § 2604(a).

[13]NIH Common Fund's Complement Animal Research In Experimentation (Complement-ARIE) program, https://www.commonfund.nih.gov/complementarie, accessed Aug. 5, 2024.

[14]When FDA qualifies an OOC drug development tool (DDT) under the Innovative Science and Technology Approaches for New Drugs Pilot Program (ISTAND) it will be available to use in any drug development program for the qualified context of use. A qualified DDT, within the stated context of use, can be relied upon to have a specific interpretation and application in regulatory review and drug development.

[15]NIH, "NIH to prioritize human-based research technologies," published April 29, 2025, https://www.nih.gov/news-events/news-releases/nih-prioritize-human-based-research-technologies, accessed April 30, 2025.

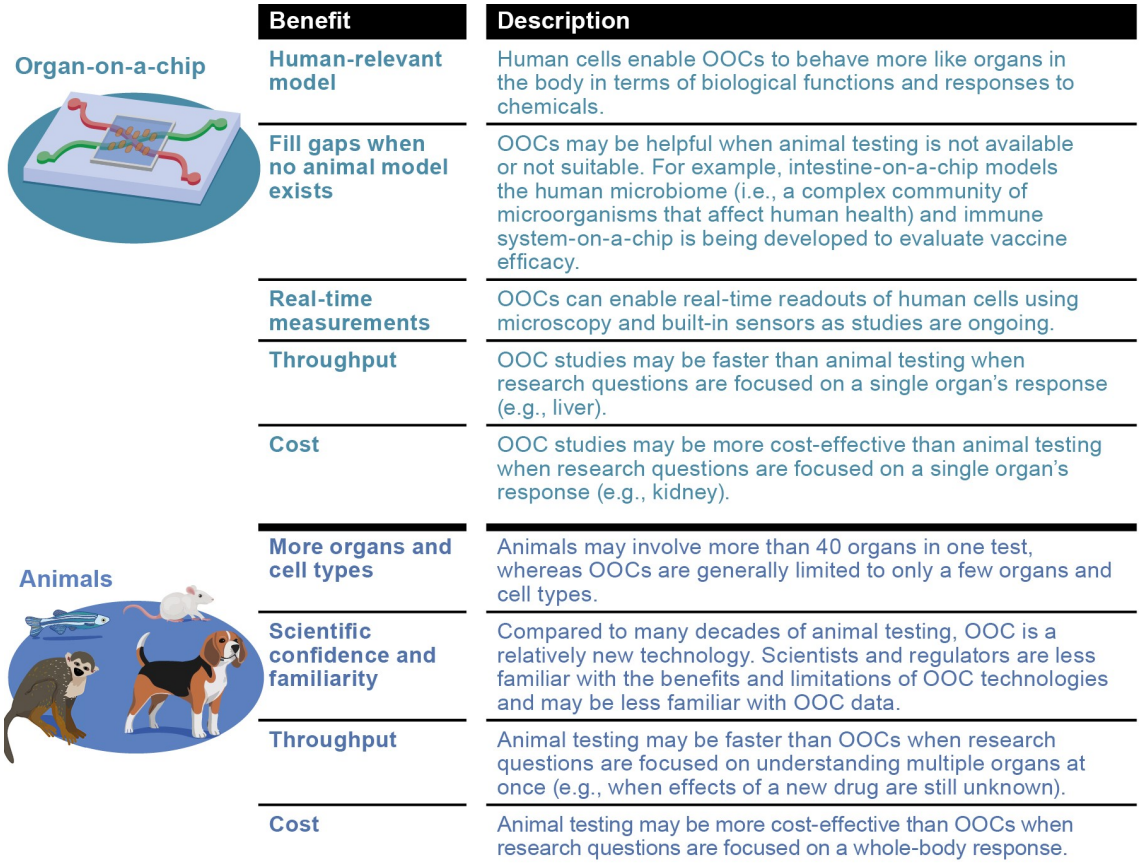
2 The State of OOC Technologies

OOC technologies complement conventional laboratory methods. They offer potential benefits but will not likely replace animal testing, at least in the near term. The field has grown rapidly in the past decade, driven primarily by investment and research from the pharmaceutical industry. Various types of OOC technologies are in use or in development, including single-organ OOCs and multiorgan OOCs.

2.1 OOCs will likely complement but not fully replace animal testing in the near term

OOCs complement animal testing and may provide some benefits over these models (see fig. 4) but will likely not completely replace them in the near term. OOCs can mimic the responses of certain human organs but researchers and other stakeholders do not yet have sufficient confidence in OOCs to completely replace the need for animal testing. In April 2025, FDA officials told us they envision increasing uses of OOC that could reduce animal testing in specific situations, but OOCs are not yet sufficiently developed to broadly replace animal testing.

Figure 4: How current organ-on-a-chip (OOC) technologies compare to animal testing



	Benefit	Description
Organ-on-a-chip	Human-relevant model	Human cells enable OOCs to behave more like organs in the body in terms of biological functions and responses to chemicals.
	Fill gaps when no animal model exists	OOCs may be helpful when animal testing is not available or not suitable. For example, intestine-on-a-chip models the human microbiome (i.e., a complex community of microorganisms that affect human health) and immune system-on-a-chip is being developed to evaluate vaccine efficacy.
	Real-time measurements	OOCs can enable real-time readouts of human cells using microscopy and built-in sensors as studies are ongoing.
	Throughput	OOC studies may be faster than animal testing when research questions are focused on a single organ's response (e.g., liver).
	Cost	OOC studies may be more cost-effective than animal testing when research questions are focused on a single organ's response (e.g., kidney).
Animals	More organs and cell types	Animals may involve more than 40 organs in one test, whereas OOCs are generally limited to only a few organs and cell types.
	Scientific confidence and familiarity	Compared to many decades of animal testing, OOC is a relatively new technology. Scientists and regulators are less familiar with the benefits and limitations of OOC technologies and may be less familiar with OOC data.
	Throughput	Animal testing may be faster than OOCs when research questions are focused on understanding multiple organs at once (e.g., when effects of a new drug are still unknown).
	Cost	Animal testing may be more cost-effective than OOCs when research questions are focused on a whole-body response.

Source: GAO analysis of scientific literature (data); U.S. Food and Drug Administration image licensed via BioRender.com as modified by GAO, Happypictures/Creativestore/Marina/wordspotrayal/stock.adobe.com (images). | GAO-25-107335

There are a few additional ways that OOCs may complement or reduce animal testing.

- **Internal decision-making.** At our expert meeting, experts told us that OOCs are being used by drug companies for internal decision-making. For example, an OOC could be used to assess dozens of drug candidates and identify those that show promise in humans instead of conducting these assessments using rodents.
- **Investigate follow-up questions.** FDA officials told us that researchers can use OOCs to answer follow-up questions from animal studies to investigate specific organ types. For example, an animal study might show that a drug candidate causes toxicity in a specific organ, and researchers could use an OOC to investigate how that toxicity develops.
- **Use OOCs in lieu of animals for certain standardized tests.** Officials from EPA's Office of Chemical Safety and Pollution Prevention told us that OOCs included in current Organisation for Economic Co-operation and Development (OECD) Test Guidelines are used for regulatory purposes to replace traditional tests using animals. For example, OECD Test Guidelines 431 and 439 allow for different skin OOCs as acceptable test methods to assess whether new chemicals may cause skin damage in humans.[16]

2.2 OOC offers benefits and limitations compared to other cell-based methods

OOC can complement simple cell-based methods and offers some benefits. For example, as described in section 1.3, unlike other cell-based methods, OOC enables fluid to flow across the cells and allows 3D interactions among cells in a more natural way. Similar to animals, OOC can serve as a follow-up study after a conventional cell-based screening. A benefit of OOC over other cell-based methods is that it provides a microenvironment that better simulates human physiology. For example, an expert told us that a 3D model, such as OOC, is essential for predicting thyroid toxicity because simple cell-based methods cannot sufficiently replicate organ architecture or thyroid hormone production. Several forces that cells experience in the human body are absent in simple cell-based methods, including continuous blood flow; chemical, mechanical, and electrical stimulations; and interactions with other cells. OOC mimics some of these characteristics—for example, fluid flow and cell-to-cell contact. An OOC system may also stretch or contract, which simple cell-based methods do not; and researchers have shown this is a necessary component to simulate functions of certain human organs—specifically, lung-on-a-chip and intestine-on-a-chip.[17]

However, OOC also has limitations compared with simple cell-based methods. OOCs may

[16]OECD, Test Guideline No. 431, *In Vitro* Skin Corrosion: Reconstructed Human Epidermis (RhE) Test Method (June 18, 2019); OECD, Test Guideline No. 439, *In Vitro* Skin Irritation: Reconstructed Human Epidermis Test Methods (June 14, 2021).

[17]Donald E. Ingber, "Human organs-on-chips for disease modelling, drug development and personalized medicine," *Nature Reviews Genetics* (2022), DOI: https://doi.org/10.1038/s41576-022-00466-9.

have lower throughput, can cost more, and require highly skilled staff.[18] Further, the practical benefits are not fully understood. For example, expert meeting participants told us it is often not clear when OOCs are more predictive than other cell-based methods in the absence of more large-scale studies.

2.3 OOC has seen rapid growth from drug development and other applications

OOC is an emerging technology, and the field has experienced rapid growth in the past decade. The pharmaceutical industry is one of the main driving forces of the technology's growth. Other industries, such as the chemical industry, use the technology but to a lesser extent. Advances in supporting technologies—such as stem cells, 3D printing, cell sensors, and microfluidic engineering—have also enabled OOC growth.[19]

The publication of research on the first microfluidic lung-on-a-chip in 2010 was an inflection point for the technology.[20] Since then, stakeholders from academia, industry, and federal agencies have developed OOCs to model more than 20 human tissues, organs, or organ systems. As of 2024, dozens of companies offer commercially available OOCs as products or services.

In addition to research, various stakeholders (see sec. 1.4) use OOCs for different applications, including drug development, chemical safety, and biodefense, among others.

Drug development. As seen in figure 5, drug companies can use OOCs during multiple points of drug development for different purposes, including understanding how a drug might move through the human body, safety and efficacy studies, and, potentially, personalized medicine. These studies can be done for internal decision-making such as selecting a drug candidate for further development or regulatory applications such as meeting safety requirements to begin clinical trials. One expert told us that the human relevance of OOCs may be particularly beneficial for testing certain types of drugs called biologics—for which nonhuman primates (e.g., monkeys) are typically the only appropriate species for testing.[21] At our expert meeting, experts told us that companies have begun using OOCs to assess aspects of drug safety and efficacy. In addition, FDA officials told us the agency has received limited OOC data from drug sponsors in applications to start clinical trials and has reviewed OOC data that provided some basic pharmacology information.

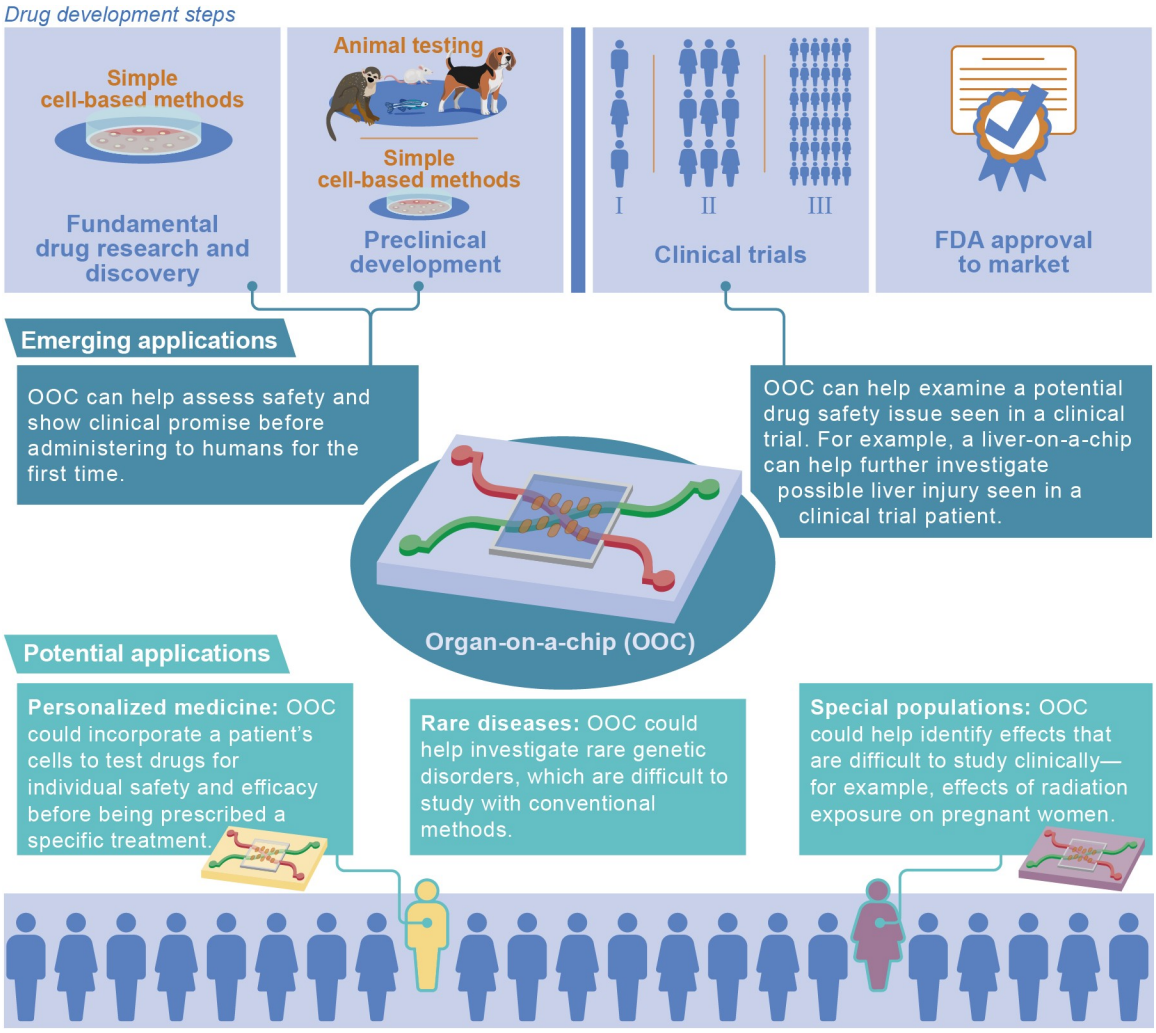
[18]Higher-throughput OOCs are in development that may be useful for screening new drug candidates more efficiently. For example, one company has shown the potential for integrating 64 microfluidic chips on a single plate while using automated handling and imaging techniques.

[19]Researchers generally use cells taken from patients to derive a special type of stem cell known as "induced pluripotent stem cells." These are different from embryonic stem cells.

[20]Dongeun Huh et al. "Reconstituting Organ-Level Lung Functions on a Chip," *Science* (2010), DOI: https://doi.org/10.1126/science.1188302.

[21]Biologics are a diverse category of products that includes vaccines and allergenic products, blood and blood components, and proteins applicable to the prevention, treatment, or cure of a disease or condition. See 42 U.S.C. § 262(i)(1). Biologics are generally derived from living material, such as the human body or a microorganism.

Figure 5: Organ-on-a-chip (OOC) and drug development



Source: GAO analysis of scientific literature (data); GAO (icons); U.S. Food and Drug Administration image licensed via BioRender.com as modified by GAO, Greenvector/Happypictures/Creativestore/Marina/wordspotrayal/stock.adobe.com (images). | GAO-25-107335

FDA has published articles discussing how novel technologies, including OOC, could help researchers address key drug development topics—such as mechanisms of action, identifying risks for special populations (e.g., pediatrics), and predicting risks that are difficult or unethical to assess in humans (e.g., carcinogenicity or developmental and reproductive toxicology).[22]

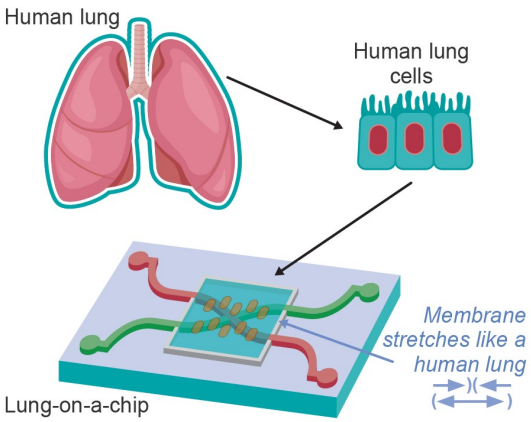
[22]The mechanism of action is how a drug or medical product produces an effect in the body. Amy Avila et al. "An FDA/CDER perspective on nonclinical testing strategies: Classical toxicology approaches and new approach methodologies (NAMs)," *Regulatory Toxicology and Pharmacology,* vol. 114 (2020), DOI: https://doi.org/10.1016/j.yrtph.2020.104662; Amy Avila et al. "Gaps and challenges in nonclinical assessments of pharmaceuticals: An FDA/CDER perspective on considerations for development of new approach methodologies," *Regulatory Toxicology and Pharmacology,* vol. 139 (2023), DOI: https://doi.org/10.1016/j.yrtph.2023.105345.

Chemical safety. The chemical industry uses OOCs for safety testing but to a lesser extent than the pharmaceutical industry, according to EPA and an expert we spoke with.

OOC holds promise for testing chemical safety, including environmental exposures in the workplace (see lung-on-a-chip text box).

OOC also holds promise in cases where clinical studies are not ethical or practical (see placenta-on-a-chip text box).

Lung-on-a-chip



What is it?

Researchers have developed organ-on-a-chip technologies that mimic key structures and functions of the human lung, such as the ability to stretch and expand to simulate breathing.

Why it matters?

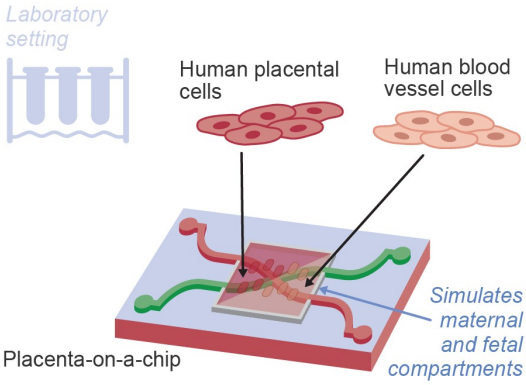
Lung-on-a-chip technologies are in development to study the potential toxicity of chemicals, such as workplace exposures to inhaled chemicals. These technologies have the potential to replace existing methods for inhalation testing using rodents. Rodent respiratory systems differ significantly from humans and therefore lung-on-a-chip technologies may provide data that better predict effects in humans while also reducing the number of animals needed.

What is the developmental status?

Lung-on-a-chip is among the most developed of all organ-on-a-chip technologies. Nearly 20 companies offer commercially available lung-on-a-chip systems. Researchers are also developing proof-of-concept lung-on-a-chip technologies for different uses—for example, to study asthma, effects of air pollution on human health, and respiratory virus infections.

Source: GAO analysis of scientific literature and 3Rs Collaborative Microphysiological Systems Technology Hub (data); U.S. Food and Drug Administration image licensed via BioRender.com as modified by GAO, Инна Харламова/Greenvector/stock.adobe.com (images). | GAO-25-107335

Placenta-on-a-chip



Note: No human fetal cells are used in these experiments.

What is it?

Placenta-on-a-chip generally includes three main parts: a maternal compartment, a fetal compartment, and a membrane in between. Each part is comprised of different cell types. Connecting the fetal and maternal compartments to fluid flow can simulate the dynamic environment of a placenta.

Why it matters?

Pregnant women are often excluded from clinical trials to test drugs because of concerns about harming the fetus, and animal testing does not adequately predict human responses. This presents ethical challenges to studying these biological processes. Early research using placenta-on-a-chip technologies has furthered understanding of the factors that affect maternal and fetal health and provided data on the toxicity, efficacy, and interactions of drugs with the placenta.

What is the developmental status?

Placenta-on-a-chip is a nascent technology that holds potential to mitigate some of the drawbacks and ethical challenges of conventional methods, such as animal testing.

Source: GAO analysis of scientific literature (data); U.S. Food and Drug Administration image licensed via BioRender.com as modified by GAO, Greenvector/stock.adobe.com (images). | GAO-25-107335

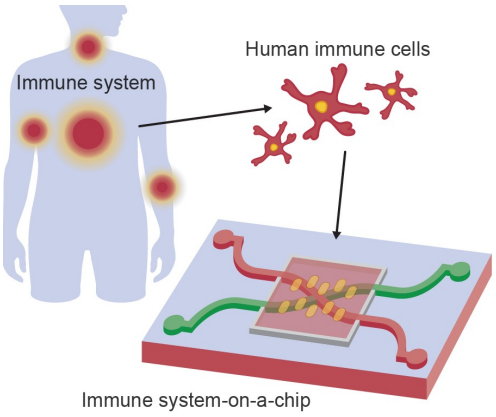
Biodefense, national countermeasures, and DOD personnel support. The Department of Defense (DOD) is interested in using OOCs to develop medical countermeasures, evaluate vaccine performance, and model biological and chemical effects to benefit civilian and military personnel.[23] The Defense Advanced Research Projects Agency (DARPA) fielded a program from 2012 through 2019 to fund OOC research, in part to better respond to biological threats.[24] As of July 2024, the Defense Threat Reduction Agency plans to have a program focused on validating OOCs as viable alternatives to animal testing and has a goal of decreasing the time and resources required to respond to biological and chemical threats (see immune system-on-a-chip text box).[25]

2.4 Single-organ OOC technologies are more mature than multiorgan OOCs

Single-organ OOC technologies are at various stages of development and, in general, are more advanced than multiorgan OOCs. See figure 2 for illustrative examples of single-organ OOCs.

Researchers, developers, and end users are creating or using various single-organ OOCs. Most OOC development activity has occurred for the heart, intestine, kidney, liver, and lung. Liver-on-a-chip is of

Immune system-on-a-chip



What is it?

The human immune system helps to maintain a healthy functioning body—including by clearing out cellular debris, keeping diseases like cancer at bay, and responding to viruses or bacteria. Researchers have developed multiple proof-of-concept immune system-on-a-chip technologies to model these processes.

Why it matters?

Immune system-on-a-chip can model how circulating immune cells respond to medical interventions, including vaccines, and biological threats such as viruses and bacteria.

Immune system-on-a-chip technologies are of particular interest to the pharmaceutical industry and the Department of Defense (DOD). Drug companies want to incorporate them into their drug development pipelines to understand how circulating immune cells interact with other organs, such as the liver, or disease processes, such as responding to tumors. DOD is investigating their potential to characterize new pathogens that could affect the warfighter. DOD officials told us that the agency is also interested in using immune system-on-a-chip to more quickly develop countermeasures against new pathogens without relying on nonhuman primates (e.g., monkeys).

What is the developmental status?

DOD officials told us that immune system-on-a-chip efforts may require at least 10 years to obtain U.S. Food and Drug Administration approval because improvements are needed to better incorporate certain aspects of the immune system.

Source: GAO analysis of scientific literature; DOD (data); U.S. Food and Drug Administration image licensed via BioRender.com as modified by GAO, Greenvector/Eveleen007/stock.adobe.com (images). | GAO-25-107335

[23]The U.S. Department of Health and Human Services—through NIH, FDA, and the Biomedical Advanced Research and Development Authority—has also conducted work using OOCs to develop medical countermeasures, which may be used in a public health emergency, among other purposes.

[24]DARPA's Microphysiological Systems program was intended to build on the limited basic research on OOCs occurring at that time. This program also included NIH's NCATS to help develop OOCs for wider use in biomedical research.

[25]The Defense Threat Reduction Agency's program is called Comparing Animal Models to Organ Tissue Equivalents—

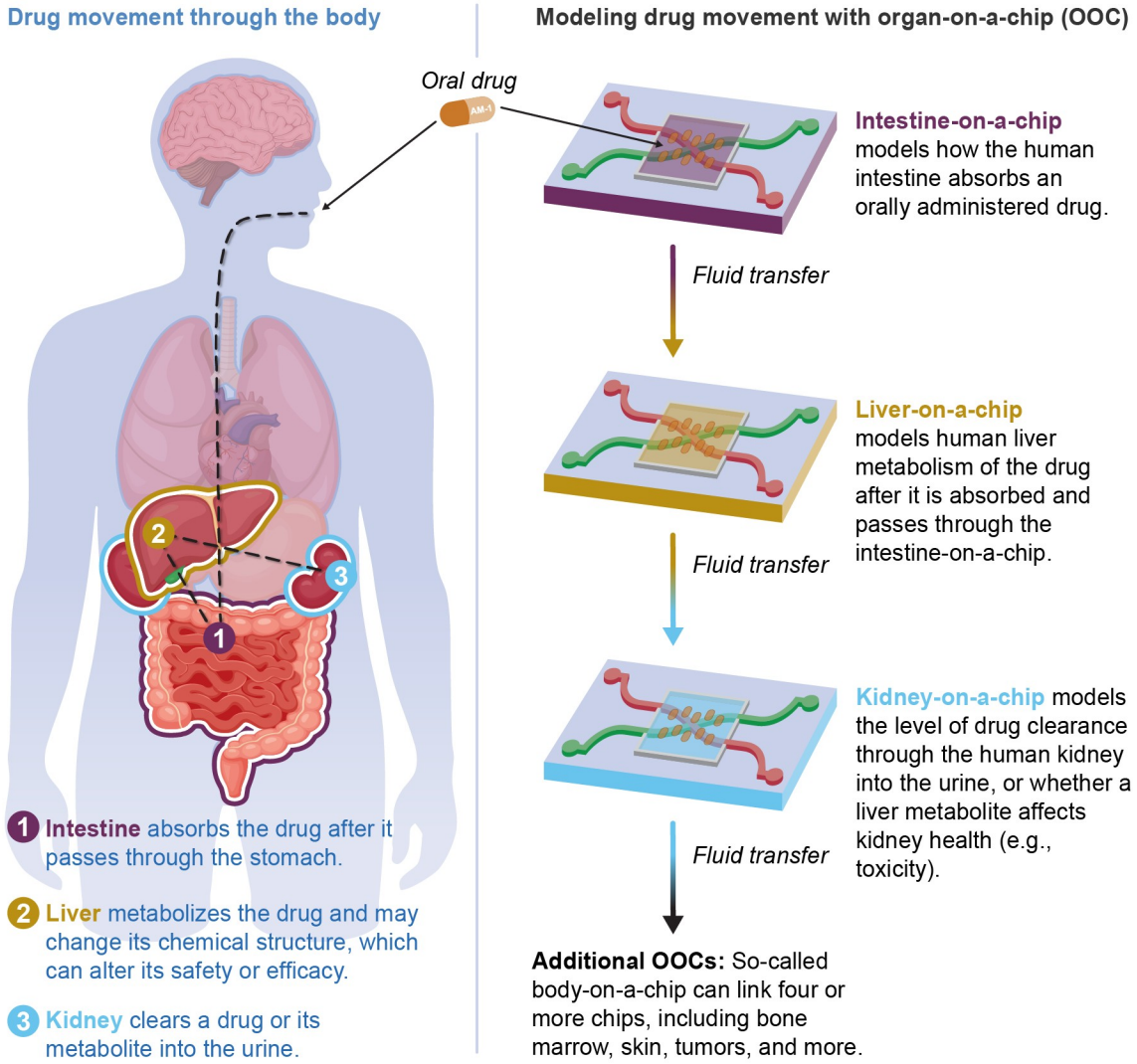
particular interest to various industries—including those that develop drugs, foods, and other consumer products—because the liver processes chemicals that enter the body through the stomach and intestine and is vulnerable to toxicity. Drug-induced liver injury has been the most frequent cause of safety-related drug withdrawals for the past 50 years and multiple OOC developers are establishing relevant liver-on-a-chip models. For example, one company has shown its liver-on-a-chip could have predicted drug-induced liver injury for 12 of 15 drugs that had previously passed animal testing but were toxic in clinical trials.[26] Despite advancements, a liver-on-a-chip that completely replicates human liver function does not yet exist.

The next generation of OOC is focused on advanced disease modelling and developing multiorgan OOC, along with other lines of effort. Sometimes referred to as body-on-a-chip, multiorgan OOC links different organs to each other on one or more systems to investigate interorgan effects. For example, multiorgan OOC can help assess secondary drug toxicity—that is, when an organ metabolizes a drug and the resulting break-down products cause a secondary negative effect. NIST told us that development of multiorgan OOC in the past 10 years has resulted in a large variety of systems. Examples of multiorgan OOCs in development include immune-tumor, the female reproductive system, and intestine-liver-kidney (see fig. 6).

referred to as CAMO. In August 2024, DOD held a 2-day workshop for government, academic, and industry stakeholders to discuss challenges, gaps, and current OOCs relevant to DOD's needs.

[26]Lorna Ewart et al. "Performance assessment and economic analysis of a human Liver-Chip for predictive toxicology," *Communications Medicine* (2022), DOI: https://doi.org/10.1038/s43856-022-00209-1.

Figure 6: Organ-on-a-chip (OOC) modeling multiple organ systems



GAO analysis of scientific literature (data); U.S. Food and Drug Administration image licensed via BioRender.com as modified by GAO, Инна Харламова/ Eveleen007/stock.adobe.com (images). | GAO-25-107335

3 Challenges to OOC Development and Use

Based on our review of the literature, interviews with experts and agency officials, and the expert discussion group, we identified six categories of challenges that may hinder the development or use of OOC technologies: (1) human cells used for OOCs, (2) resource demands for end users, (3) a lack of OOC-specific standards, (4) a lack of benchmarks and validation studies, (5) limited data sharing, and (6) regulatory uncertainties.

3.1 Human cells used for OOCs

Obtaining reliable human cells is a key requirement to use OOCs. However, acquiring human cells of sufficient quantity, quality, and diversity is challenging.

Cell sourcing and quality. The availability of high-quality human cells is limited. Primary human cells—that is, cells isolated directly from people—often require research contracts with hospitals or purchasing from other sources that have limited supply. For example, primary human brain cells must be recovered from a surgery or cadaver. Researchers can use certain cells—known as induced pluripotent stem cells—to produce a steady source for some cell types, which can help mitigate the availability challenge in some cases.[27] However, induced pluripotent stem cells will not fully address the cell sourcing challenge because of technical difficulties for certain cell types that prevent them from behaving like adult cells, among other reasons. In addition to the sourcing challenge, quality can be an issue. For example, two experts told us that only 10 percent to 20 percent of donor primary cells they purchase are of high enough quality to use in OOC studies.[28]

Diversity of cells. Available human cells often lack sufficient genetic diversity, leading to OOC results that may not properly reflect the demographic diversity of populations. One expert told us more than 70 percent of primary and induced pluripotent stem cells come from White donors. Genetic diversity is important for accurately predicting human outcomes and assessing immune responses that might apply to national and global populations. A lack of genetic diversity in cell sources is a challenge for all human cell-based methods, including OOCs.

3.2 Resource demands for end users

OOC end users face challenges related to resource requirements, including high costs, time-intensive testing processes, requirements for highly trained staff, and technology availability.

[27]Induced pluripotent stem cells are derived from human body cells—often from blood or skin taken from patients—that researchers can reprogram to create different cell types (these cells can be derived from body cells other than reproductive cells). For example, researchers can use these cells to generate heart muscle cells in the lab for heart-on-a-chip technologies. Induced pluripotent stem cells are different from human embryonic stem cells.

[28]Researchers can also use established cell lines, which are lab-modified cells that can be produced in virtually unlimited supply and are intended to behave similarly to primary cells. However, established cell lines are normally not preferred in OOCs due to concerns about quality and the need to validate them against primary cells.

High costs. OOCs require large financial investments that may prevent many research labs from adopting the technology. For example, end users can face start-up costs of over $150,000—including to acquire the initial chips, which can only be used once, and other supplies—and still lack confidence in the results. Even after making the initial investment, users may face thousands of dollars in recurring costs, including to obtain an ongoing supply of chips and human cells. These costs are higher than simple cell-based methods, and experts told us they are often uncertain whether the added complexity of OOCs is worth the extra cost. According to an expert, many institutions already have sunk costs into animal facilities, so the extra costs and space requirements for OOC studies can also be challenging to justify to leadership. Experts told us that OOC studies may be more cost-effective than animal testing when studies are focused on a single organ's response (e.g., liver), but not in cases when researchers need to assess whole-body responses (e.g., comprehensive safety studies for new drugs).[29]

Time-intensive testing processes. Preparing and carrying out OOC experiments is time intensive and end users are still optimizing their testing approaches. One end user told us it takes about 10 days to prepare and position human cells for a new OOC experiment before any testing takes place. These time demands are higher for OOCs compared with simple cell-based methods due to the complexities of growing multiple cell types, among other reasons. Then, according to this end user, an OOC experiment can take approximately 10 more days and require three full-time employees to operate, which is generally more resource-intensive than simple cell culture. As is the case with many new technologies, experiments can take even longer if team members lack the proper expertise. For example, an expert told us that OOC experiments can take as long as 8 weeks in the hands of less experienced staff. There may also be technical difficulties that add more time—for example, bubbles in the fluid-filled channels.

Highly trained staff. Given the complexities of OOC, these technologies require staff with a high level of expertise to operate. Staff with specific qualifications—such as relevant engineering and biomedical research skills—are in short supply, in part due to the newness of the technologies. In addition, one expert told us training existing staff can take at least 1 year.

By working with contract research organizations, end users can potentially mitigate the need to hire or train staff. However, one end user told us that if they use a contract research organization, they usually conduct a pilot project to confirm the new model fits their research goals, which still requires trained staff. Additionally, a different end user told us that using a contract was slower than testing the OOCs in house because the end user was unable to quickly adapt and troubleshoot.

Technology availability. Choosing a commercially available OOC to acquire can

[29]Due to limited data on costs and factors that affect costs relative to other methods, we were not able to determine the magnitude of these differences.

also be resource-intensive, and many OOCs are not commercially available. For example, there are multiple commercially available liver-on-a-chip technologies, but an end user may not know which one is appropriate without extensive testing in house. Additionally, some specialized OOCs—for example, organs that are not commonly studied like the gallbladder—have been described in peer-reviewed journals but may not be available to purchase.

3.3 Lack of OOC-specific standards

A lack of standards specific to OOCs may cause challenges with communication, reproducibility of results, and use of the technologies. However, NIST officials told us that establishing OOC-specific standards is difficult because the technology is complex and rapidly evolving. Additionally, experts told us that standardizing certain aspects of OOCs—such as the various chip sizes and number of fluid-filled channels on each chip—may potentially limit the field's ability to innovate. NIST told us that standardization efforts related to multiorgan OOCs are urgently needed. In general, experts agreed that some standardization could facilitate OOC implementation and innovation.[30]

Experts also told us that establishing standard terminology and definitions could lead to clearer communication among relevant stakeholders. NIST works with the OECD to coordinate global standardization related to OOC. NIST told us it is also coordinating efforts within the International Organization for Standardization (ISO) to develop comprehensive OOC standards related to vocabulary, measurement, biological components, engineering, and data. FDA informed us that it is also actively engaged in these efforts within ISO.

International efforts with human organ-on-a-chip (OOC) standardization

In July 2024, a European standardization organization published an OOC roadmap that outlined priority recommendations for standardization. This roadmap, created over 2 years with the active participation of around 120 experts, made recommendations on the need to standardize terminology, aspects of the system hardware, and requirements for experimental design to achieve reliable data. It also described that the lack of standards slows down innovation and negatively affects reproducibility and comparability of OOC results. Additionally, the roadmap highlighted some existing standards that were not specifically designed for OOCs but may be relevant; however, it is unclear whether these standards are being applied in OOC systems.

Following the release of the OOC roadmap, the International Organization for Standardization (ISO) formed a subcommittee to advance standardization for several aspects of OOCs, including terminology, biological components, and characterization of materials and processes. As of February 2025, the ISO subcommittee has three international standards under development, including on the quality control of cells and vocabulary used for OOCs.

Source: Focus Group Organ-on-Chip Standardization Roadmap, The European Committee for Standardization and the European Committee for Electrotechnical Standardization; GAO analysis of ISO information. | GAO-25-107335

3.4 Lack of benchmarks and validation studies

Even with more than a decade of publications showing the potential for OOCs, end users are in the early stages of adopting the technology and still rely heavily on conventional lab methods. Increasing adoption of OOCs will depend on end users understanding how

[30]In 2022, a group of 200 international stakeholders at a workshop hosted by FDA and a drug company consortium agreed that developing standards or guidelines for every OOC context of use would be difficult, but stakeholders could consider developing broadly applicable standards that can be applied regardless of context of use or specific OOC.

these technologies compare with conventional methods and data from clinical trials. However, such comparisons are challenging due to the lack of benchmarks and validation studies.

Benchmarks. Benchmarks are defined points of comparison to measure results against. Examples of benchmarks include outcomes from testing reference compounds—that is, drugs or chemicals that have known effects in humans—that can help researchers understand whether OOCs predict responses in people. Benchmarks are necessary to compare the performance of commercially available OOCs to each other; to conventional methods, such as animal testing; or to known human outcomes, such as specific organ-related toxicities (e.g., drug-induced liver injury) from clinical trial data. However, these types of benchmarks are often not available for OOC, which can hinder both the development and use of the technology. For example, experts told us there are too few reference compound lists available for OOCs, making it challenging to gain confidence in OOCs for specific contexts of use.[31]

There are some ongoing efforts to address this challenge but they are currently insufficient or face limitations. For example, in 2021 FDA published a list of reference compounds with known positive and negative outcomes that could help researchers assess where OOCs might predict responses related to reproductive and developmental toxicities in people.[32] In addition, between 2010 and 2017, three drug companies provided NCATS with a list of 120 reference compounds, but the compound library was expensive to establish and difficult to manage since the compounds were typically not commercially available, according to officials.

Validation studies. The lack of validation studies for OOCs—that is, assessments about their accuracy, reliability, and relevance—have made stakeholders uncertain whether these technologies can provide useful results. Examples of validation studies include assessing the performance of OOCs using reference compounds or in relation to existing relevant toxicity data, which could in turn increase scientific confidence.[33] However, sufficient validation studies have rarely been conducted for OOCs, even those that are commercially available, and when they have been conducted the results are often not shared with all relevant stakeholders. For example, EPA officials told us that more validation studies are needed to gain sufficient confidence in using OOCs to assess chemicals in commerce, specifically when the OOCs were developed for pharmaceutical testing. This means that end users often lack key information about which OOC best fits their research needs and therefore must conduct such studies in house.

[31]FDA defines context of use as the intended manner and purpose of use for a test method, such as an OOC. See https://www.fda.gov/science-research/advancing-alternative-methods-fda/about-alternative-methods, accessed April 14, 2025. For example, a context of use for a liver-on-a-chip system may be to predict drug-induced liver injury for specific types of chemicals.

[32]FDA, *S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals: Guidance for Industry* (May 2021).

[33]There are internationally harmonized validation frameworks, such as OECD Guidance Document 34, that provide detailed guidance on conducting validation studies.

Additionally, a single OOC system may have different contexts of use, which would require validation studies for each. For example, a specific lung-on-a-chip may have been extensively validated for its ability to assess the efficacy of drugs for pulmonary edema, but a different lung-on-a-chip would need to be sufficiently validated for another lung-related context of use, such as pulmonary fibrosis. End users often need to conduct such validation studies for each new context of use to have sufficient scientific confidence in the results—including for internal decision-making or regulatory filings.

The Texas A&M Tissue Chip Validation (TEX-VAL) Consortium is an example of an organization that performs OOC validation studies for various stakeholders (see text box). EPA told us that TEX-VAL gave the agency insight into technical and quality control issues that may arise with particular OOCs, which helped to guide selection of OOC systems and informed best practices to mitigate technical challenges.

The Texas A&M Tissue Chip Validation (TEX-VAL) Consortium

TEX-VAL is a human organ-on-a-chip (OOC) validation center started in 2016 with funding from the National Institutes of Health (NIH). From 2020 to 2023, TEX-VAL worked to replicate published findings on and assess the robustness of OOCs in more than 100 studies, including OOCs that model the kidney, liver, intestine, blood-brain barrier, lung, and female reproductive system.

Members pay an annual fee and provide two or three scientists to participate in monthly meetings and communicate their organization's needs and testing goals. In exchange, members gain exclusive access to all TEX-VAL data for 1 year following a study's completion, after which the data become public. Members also share OOC best practices and receive technical and scientific support from TEX-VAL scientists.

Since 2020, the Consortium has been a mix of companies and government agencies. NIH has participated every year from 2020 to 2025. The Environmental Protection Agency was a member from 2020 to September 2023, and the agency told us that, due to budget cuts, it left after its contract with TEX-VAL ended. As of 2025, TEX-VAL had seven members, including drug and chemical companies.

Source: GAO analysis of TEX-VAL information; EPA. | GAO-25-107335

3.5 Limited data sharing

Developers and end users can be reluctant to or may lack capacity to share their OOC research findings, which can hinder understanding and validation of the technology. Experts told us companies are hesitant to share information due to concerns about intellectual property and loss of competitive advantages. Additionally, one end user from a drug company told us they conduct OOC validation studies in house and take the time to publish the results, but other companies do not normally publish the results from their OOC studies. Companies are also hesitant to submit OOC data to regulators unless the data are overwhelmingly positive because they are concerned any negative data may jeopardize an application's chance of approval.

Experts we spoke with indicated there have been some efforts to increase OOC data sharing within the field. For example, in 2017 NCATS supported the creation of a database at the University of Pittsburgh as a central archive for data generated in OOC validation centers, such as TEX-VAL. It was designed to aggregate and manage data from OOCs and related technologies and evaluate them against reference data. As of December 2024, NCATS told us that the database was acquired by a private company and was transitioning

the data from the university to private management.[34]

Safe harbor designation for organ-on-a-chip (OOC) data

What is it?

Safe harbor designation, or voluntary data submission, is a way for companies to submit exploratory data to regulators without the risk of regulatory decisions being made based on those data.

Safe harbor previously used for genomic data

The U.S. Food and Drug Administration (FDA) used this approach beginning in 2004 to encourage companies to submit genomic data, which includes aspects of DNA, to gain understanding of this type of data. Within 5 years, FDA received over 40 data submissions and had more than 35 meetings with companies. According to a review of this program, these meetings led to mutually beneficial discussions between FDA and companies and helped the companies integrate genomic data into drug development pipelines.

Potential use of safe harbor for OOC data

Experts told us that a safe harbor designation for OOC data may help encourage more inclusion of such data in regulatory filings. For example, one expert told us this could help companies gauge the receptivity of FDA toward OOC data necessary to support regulatory applications. A 2021 survey of over 20 drug companies showed that companies thought safe harbor could help address their concerns with regulatory bodies misinterpreting or overinterpreting OOC data.

FDA officials told us that they are not aware of any plan to create a safe harbor designation for OOC data. These officials told us it may be difficult to allocate resources for this purpose and could present new challenges for FDA, specifically if OOC data raised safety concerns. The European Medicines Agency, which regulates drugs for the European Union, began offering safe harbor for OOC data in Europe in 2016.

Source: GAO analysis of scientific literature. | GAO-25-107335

Multiple consortia encourage data sharing among members but still face obstacles. For example, one consortium promotes collaboration and data sharing, but this collaboration is often ad hoc, and their membership is limited to the pharmaceutical industry. This consortium has held at least two workshops with FDA and pharmaceutical companies and has published multiple papers on select topics related to OOCs.[35]

3.6 Regulatory uncertainties

According to experts, the OOC field faces challenges related to regulatory uncertainties, including regulators' understanding of OOCs, unclear FDA regulatory guidance and messaging, and FDA's nascent qualification program.

Regulators' understanding of OOCs. Regulatory agencies have many years of training and experience reviewing data from conventional laboratory methods, such as 2D cell models and animals, but officials told us they have less familiarity with new methodologies, including OOCs. Furthermore, regulatory agencies need trained staff to interpret OOC data for decision making. GAO has previously reported on workforce constraints at both FDA and EPA, which can affect regulatory reviews.[36]

[34]NCATS told us that NIH-funded investigators who generate or submit data will continue to receive free access, whereas a subscription fee would be required for those not submitting data.

[35]For example, see Szczepan W. Baran et al. "Perspectives on the Evaluation and Adoption of Complex In Vitro Models in Drug Development: Workshop with the FDA and the Pharmaceutical Industry (IQ MPS Affiliate)," *ALTEX - Alternatives to Animal Experimentation* (2022), DOI: https://doi.org/10.14573/altex.2112203; Lorna Ewart et al. "Navigating tissue chips from development to dissemination: A pharmaceutical industry perspective," *Experimental Biology and Medicine* (2017), DOI: https://doi.org/10.1177/1535370217715441.

[36]GAO, *EPA Chemical Reviews: Workforce Planning Gaps Contributed to Missed Deadlines,* GAO-23-105728 (Washington, D.C.: February 2023); GAO, *FDA Workforce: Agency-Wide Workforce Planning Needed to Ensure Medical Product Staff Meet Current and Future Needs,* GAO-22-104791 (Washington, D.C.: January 2022).

FDA officials told us they are currently working to better understand OOC performance from a regulatory perspective, including how to interpret results and understand reproducibility. FDA has assessed OOC data on a case-by-case basis in its regulatory reviews—including in applications to begin clinical trials. However, FDA officials told us that having trained staff to evaluate and interpret OOC data is the largest barrier the agency faces with regards to OOC given the newness and rapidly changing nature of the technology. The agency is evaluating various OOCs for the potential regulatory utility based on specific contexts of use, including their benefits and limitations, and engaging in workshops with developers and end users. In the near term, FDA officials told us that OOCs may complement conventional laboratory methods and, in some cases, possibly eliminate specific animal tests. For example, FDA officials told us that OOCs may help replace certain animal tests that assess aspects of liver toxicity. In addition, when animal tests or clinical trials show toxicity in a specific organ, FDA officials told us OOCs may be used to investigate how that toxicity developed. This could allow the drug companies to better understand the drug's utility for specific applications or subpopulations.

In April 2025, FDA released a roadmap that describes how the agency might reduce its reliance on animal testing for drug safety studies in favor of validated animal alternatives, such as OOC.[37] The roadmap focuses on safety evaluations for monoclonal antibodies (a type of biologic) and describes a stepwise approach to reducing animal testing more broadly. In the roadmap, FDA says it will provide training workshops to individual agency staff on interpreting OOC data, highlight successful cases of using animal alternatives, and maintain open dialogue with industry, academia, and nongovernment organizations, among other things.[38]

EPA is also working to better understand OOC's benefits and limitations. Between 2017 and 2023, EPA received submissions with hundreds of studies reporting data from OOCs that assess skin and eye hazards using internationally accepted test methods validated by OECD. However, applying OOCs to other environmental health and chemical safety contexts of use is difficult because many OOCs are developed for pharmaceutical and other biomedical purposes, according to officials. In addition, EPA officials told us that the agency needs additional funding and training for staff to understand and interpret OOCs for regulatory decision making. For example, officials said that data generated from OOC are often atypical compared with data from animal models and may require special training for risk assessors to feel confident in interpreting OOC data.

Unclear FDA regulatory guidance and messaging. Although FDA has published recent statements communicating its support for replacing and reducing animal testing where appropriate, and using alternatives to

[37]FDA, *Roadmap to Reducing Animal Testing in Preclinical Safety Studies* (April 2025).

[38]On April 10, 2025, FDA announced that it will host a public workshop with federal partners later in 2025, among other things. See FDA, "FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs," published April 10, 2025, https://www.fda.gov/news-events/press-announcements/fda-announces-plan-phase-out-animal-testing-requirement-monoclonal-antibodies-and-other-drugs, accessed April 16, 2025.

animal studies such as OOCs, the agency has not published guidance specific to OOCs.[39] FDA told us that its Office of New Drugs within the Center for Drug Evaluation and Research plans to publish guidance regarding a broader use of OOCs and related technologies in drug applications but the timeline is unknown. FDA's April 2025 roadmap signals a more proactive stance toward replacing and reducing animal testing, where appropriate, using alternatives such as OOCs, but it did not describe precise types of studies or data FDA would like to see. FDA officials told us that the specific limitations of each OOC and its context of use will define the studies needed for OOC validation. Officials also told us that additional OOC-related guidance for drug sponsors would be determined by the relevant FDA review team for a specific application.

Selected developers and end users told us they do not fully understand which data they should submit to FDA for regulatory submissions. For example, one end user from a drug company told us that companies would like more clarity from FDA on what is needed for OOC studies to show equivalency with conventional methods. In addition, another end user from a drug company told us they have received different advice depending on the individual staff they communicate with at FDA. In April 2025, this same end user told us that FDA's roadmap and news release indicated different messaging compared to recent interactions with the agency. Two other end users from drug companies expressed optimism about the roadmap but emphasized the remaining work necessary to validate these models.[40]

FDA's qualification program is in the early stages. As of December 2024, no OOC has been qualified by FDA for use in regulatory review. However, developers can apply to have their systems qualified for specific contexts of use through FDA's Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program, which the agency established in 2020.[41] FDA officials told us that OOC developers have had challenges crafting appropriate contexts of use for their ISTAND applications and, in some cases, FDA worked with these developers to resubmit improved versions. In September 2024, ISTAND accepted its first letter of intent for an OOC—a liver-on-a-chip system—designed to predict drug-induced liver injury for certain drug candidates, which is step one of a three-step qualification process. If this liver-on-a-chip is qualified by FDA, drug sponsors may use it for any drug development programs for that specific context of use.

[39]In addition to FDA's April 2025 roadmap and news release mentioned above, see Chad P. Nelson et al. "Advancing alternative methods to reduce animal testing," *Science* (2024), DOI: https://doi.org/10.1126/science.adg6228.

[40]We followed up with three selected end users to obtain their views on FDA's April 2025 roadmap and news release.

[41]The ISTAND program was established pursuant to section 3011 of the 21st Century Cures Act of 2016. Pub. L. No. 114-255, tit. III, subt. B, § 3011, 130 Stat. 1033, 1086-91.

4 Policy Options for OOC Technologies

We identified six policy options that policymakers—including legislative bodies, government agencies, academics, OOC developers, end users, and other groups—could consider taking to help enhance benefits or address challenges to the development or use of OOCs. We identified these policy options through meetings with experts and our review of the literature. This list is not exhaustive but can provide policymakers with a broader base of information and examples for decision-making. For each policy option, we present a table with multiple potential implementation approaches, opportunities the action may present, and factors to consider. The policy options we identified include (1) supporting efforts to increase access to diverse, high-quality human cells, (2) supporting standards development for OOC, (3) encouraging more research and development of benchmarks and validation studies, (4) creating or participating in mechanisms for data sharing, (5) providing additional regulatory guidance, and (6) maintaining the status quo.

4.1 Policy Option: Support efforts to increase access to diverse, high-quality human cells

Challenge. A lack of human cells in sufficient quantity, quality, and diversity could limit the use and adoption of OOC. Policymakers wishing to address this challenge could support efforts to increase access to diverse, high-quality human cells (see table 1).

Table 1: Potential implementation approach to support efforts to increase access to diverse, high-quality human cells

Potential Implementation Approach	Opportunities	Considerations
Federal entities, together with academic and industry stakeholders, could support the establishment of high-quality cell banks and biospecimen repositories that incorporate population diversity.	Could provide developers and end users with a supply of diverse human cells for future organ-on-a-chip research. Current efforts to establish cell banks for related technologies may provide a model for these efforts.	May require a high level of stakeholder coordination, additional resources, and scientific expertise. May require additional standardized cell protocols and reference materials.

Source: GAO. | GAO-25-107335

4.2 Policy Option: Support standards development for OOC

Challenge. A lack of OOC-specific standards may negatively affect innovation, communication, and the reproducibility and comparability of results—making it more difficult to use the technologies. Policymakers wishing to address this challenge could support standards development (see table 2).

Table 2: Potential implementation approaches to support standards development for OOC

Potential Implementation Approach	Opportunities	Considerations
Standards-coordinating bodies, in collaboration with developers, end users, regulators, and others, could help determine the need for global organ-on-a-chip (OOC) standards and help establish agreement on minimum standards and acceptance criteria, as appropriate.	Could improve communication about key concepts and the reproducibility and comparability of results. Could increase understanding and lower the barrier to using OOCs for new users. Could support more widespread use of OOCs.	Standards development is difficult for emerging technologies such as OOC because the systems are rapidly evolving, and standards require broad stakeholder consensus. Establishing standards too early could stifle innovation and competition. May require a high level of effort and collaboration between standards-coordinating bodies, developers, end users, regulators, government agencies, and relevant consortia and international bodies.
A government agency could convene stakeholders within U.S.-based government agencies, academia, and industry to form a working group to address the specific needs for U.S. standards.	Could build upon existing international efforts in the European Union and elsewhere. Could potentially reach agreement sooner on what is needed within the U.S. versus what is needed for global harmonization.	Additional coordination may be required to harmonize these efforts with international standards working groups or technical committees.
Drug and chemical companies could standardize formats for OOC data submission to regulators.	Regulators may be able to uniformly assess OOC data, which may accelerate regulatory review and build scientific confidence.	Could reduce companies' flexibility in submissions or be too restrictive. Regulators may require companies to submit data in a specific format. Data submission to regulators is often proprietary and not made public, therefore it may not benefit all OOC stakeholders. Could be dependent on adherence of OOC component providers, such as cell banks and drug suppliers, to reporting requirements.

Source: GAO. | GAO-25-107335

4.3 Policy Option: Encourage more research and development of benchmarks and validation studies

Challenge. End users and regulators lack sufficient benchmarks and validation studies necessary to gain scientific confidence in OOCs and understand how these technologies compare with conventional methods and data from clinical trials. Policymakers wishing to address this challenge could encourage research and development of benchmarks and validation studies (see table 3).

Table 3: Potential implementation approaches to encourage research and development of benchmarks and validation studies

Potential Implementation Approach	Opportunities	Considerations
Relevant funding agencies could provide more funding to academics and companies for organ-on-a-chip (OOC) research, specifically to validate OOCs for priority contexts of use.	Could help to identify relevant benchmarks to validate OOCs for specific contexts of use. Could increase the number of published validation studies and lead to increased scientific confidence in OOCs. Could help train scientists in understanding and operating OOCs.	Investments in OOCs may reduce available funding for other technologies. Defining priority contexts of use will require input from and coordination with end users, such as drug or chemical companies.
Relevant funding agencies could create guidance that encourages the inclusion of human-relevant data, including OOC data, in grant applications.	Could signal that funding agencies recognize the need for additional benchmarking and validation studies.	Peer reviewers at funding agencies are primarily versed in animal studies, so there may be a need to train peer reviewers on OOC technology and data.
Drug and chemical company leadership could provide support in terms of time and money for continued OOC studies and validation efforts.	Could increase scientific confidence in OOCs for more applications. Could increase staff expertise in understanding and operating OOCs.	Companies may be hesitant to further invest because there is uncertainty in whether the validation studies could provide useful results and increase confidence.
A public-private partnership or other consortium could collaborate with federal agencies and companies to create reference compound lists for specific contexts of use.	For drug companies, a reference compound list could help researchers understand whether an OOC model is predictive of human responses to new drugs. For chemical companies, a reference compound list could allow researchers to compare the performance of their OOC model to conventional methods. Reference compounds for specific contexts of use could be considered for inclusion in regulatory guidance.	One list may not cover all aspects of a context of use, and users of these reference compounds would need to consider the specific needs of regulatory agencies. May be challenging due to potential issues regarding ownership and use of the compound.

Potential Implementation Approach	Opportunities	Considerations
Academia and industry could facilitate the U.S. Environmental Protection Agency's (EPA) participation in the development and refinement of OOC through public-private partnerships.	Could provide EPA an opportunity to communicate their unique needs compared to the biomedical space. Could lead to validated OOC models for chemical assessments.	Could require resources to validate models for EPA's use that were originally intended for academic or basic research purposes.
Government agencies, academia, and industry could collaborate to publish peer-reviewed articles that describe OOC validation methods and results.	Could demonstrate utility of OOCs across sectors. Could help move OOC from the experimental phase toward inclusion in regulatory applications.	Stakeholder collaboration can be complex and require high levels of coordination and resources. Publications may be viewed as opinion pieces or recommendations rather than as benchmarks or requirements.

Source: GAO. | GAO-25-107335

4.4 Policy Option: Create or participate in mechanisms for data sharing

Challenge. Developers and end users are reluctant to share data with different parties, including regulators, or do not share data with other stakeholders because of limited capacity. In both cases, the lack of data sharing hinders growth and understanding in the field. Policymakers wishing to address this challenge could create or participate in mechanisms for data sharing (see table 4).

Table 4: Potential implementation approaches to create or participate in mechanisms for data sharing

Potential Implementation Approach	Opportunities	Considerations
Organ-on-a-chip (OOC) developers and drug companies could participate in precompetitive efforts to share OOC data freely, such as sharing data through an industry trade group, nonprofit, or other trusted third party.	Could help end users and regulators assess the robustness of OOC. Could facilitate the development of benchmarks by sharing comparisons of processes and studies. Could increase alignment and engagement among relevant stakeholders.	Could require significant stakeholder coordination and resources. Companies may need additional incentives to participate for fear of losing a competitive advantage. May require an assessment of which OOC methods would be most likely to benefit. May depend on the development of standardized formats for reporting data.
OOC developers and drug and chemical companies could publish successful case studies that describe OOC experimental designs and how OOC data were used for internal decision-making or in regulatory filings. Companies could then make those data accessible.	Could build confidence in and aid adoption of OOC. Could save time and resources by avoiding duplicative efforts, allowing the field to advance more quickly and efficiently.	Could require additional resources to compile and submit results for publications. Companies may be hesitant to share strategies or proprietary data.

Potential Implementation Approach	Opportunities	Considerations
The U.S. Food and Drug Administration and U.S. Environmental Protection Agency could offer incentives to submit OOC data, such as providing expedited review of regulatory packages that include OOC data.	Could lead to increased regulatory submissions that include OOC data, which could increase regulators' familiarity and confidence in the data.	Could require regulatory agencies to define what constitutes an OOC as opposed to other alternatives to conventional methods. Regulatory agencies may be constrained by workforce capacity to offer such expedited reviews.

Source: GAO. | GAO-25-107335

4.5 Policy Option: Provide additional regulatory guidance

Challenges. Developers and end users are uncertain about what regulators need to see in submissions that include OOC data for specific applications. There is also a lack of regulatory guidance specific to OOC. Policymakers who wish to address these challenges could take actions that provide additional regulatory guidance (see table 5).

Table 5: Potential implementation approaches to provide additional regulatory guidance

Potential Implementation Approach	Opportunities	Considerations
Congress could increase the amount of agency funding specifically targeted to recruit and train regulatory staff to prepare guidance and review organ-on-a-chip (OOC) data for regulatory decisions.	Targeted staff training could increase regulatory agencies' scientific confidence in OOC. Additional staff could result in more timely and productive interactions between regulators and developers or end users.	Regulatory agencies may still have difficulties recruiting and retaining a trained workforce—for example, due to pay disparities with the private sector.
The U.S. Food and Drug Administration (FDA) and U.S. Environmental Protection Agency (EPA) could create guidance that encourages the inclusion of human-relevant data, such as OOC data, in applications to begin clinical trials or new chemical risk assessments.	Could help developers and end users better understand what data they need to submit to regulators. Could reduce variability in feedback individual regulatory staff provide to developers and end users. Could further signal regulators' openness to receiving human-relevant data, including OOC data, into regulatory decision-making.	Regulatory agencies may not want to draft specific guidance for OOC before they fully understand the technology or how it will be used. Developers and end users may still be hesitant to submit OOC data to regulators out of concern that it may jeopardize a regulatory application's chance of approval.
FDA and EPA could publish scenarios for which it has accepted OOC as a replacement for animal studies and the reasoning behind their acceptance.	Could help OOC developers and end users move forward with validating certain OOCs, which could facilitate further development. Could provide additional details and transparency beyond what FDA currently publishes.	The proprietary nature of applications submitted to regulatory agencies could make it challenging for them to share details of those applications. Could require regulatory agencies to dedicate resources to these new efforts.

Potential Implementation Approach	Opportunities	Considerations
FDA and EPA could provide detailed guidance on how specific OOCs can more readily replace a conventional laboratory method.	Could increase data transparency and communication between regulators and end users. Clarity from regulators on appropriate use cases within their regulatory purview could build confidence in the models and increase regulatory experience with these data.	This approach may not be helpful for certain OOC use cases. Standardized test guidelines that include OOC may be needed before regulators can develop such guidance. Guidance that is too specific could constrain developers and end users.
A public-private partnership could coordinate a working group where regulators interact regularly with OOC end users at all stages of readiness.	Could provide an opportunity for regulators to provide early input and feedback, which could clarify requirements for regulatory acceptance of OOC data.	Collaboration with regulators can be complex. Though stakeholders often request regulator participation, there can be tension when regulators are too involved with a project.

Source: GAO. | GAO-25-107335

4.6 Policy Option: Maintain the status quo

Current efforts (the status quo) may help address some of the challenges identified in this report. However, other challenges may remain unresolved or potential benefits may not be realized. Policymakers could sustain current efforts that may help mitigate challenges to the use and adoption of OOC (see table 6).

Table 6: Potential implementation approaches to maintain the status quo

Potential Implementation Approach	Opportunities	Considerations
Organ-on-a-chip (OOC) developers and end users could continue to use technologies that are currently available. Government entities, academic institutions, and industry could continue current research and validation efforts. OOC stakeholders could rely on current data sharing efforts, such as workshops and published papers from trade groups and other organizations.	Could allow resources to be used for other purposes. Current efforts to address cell sourcing issues, develop standards, benchmark and validate OOC models, share data, and provide regulatory clarity may improve on their own as the technology advances.	Currents efforts may not fully address the challenges described in this report. Until the challenges in this report are addressed, companies may continue using animals when it is cheaper and faster than developing confidence in OOCs. Developers, end users, and regulators may continue to face challenges in understanding the results from OOCs and potential of the technology. Developers may have difficulties advancing OOCs to the market. Europe may continue to advance standards development for OOC. Technologies may be more likely to fail in regulatory submissions due to a lack of clarity and guidance.

Source: GAO. | GAO-25-107335

5 Agency and Expert Comments

We provided a draft of this report to the U.S. Department of Health and Human Services (Food and Drug Administration and National Institutes of Health); the U.S. Department of Defense; the U.S. Department of Commerce (National Institute of Standards and Technology); and the U.S. Environmental Protection Agency with a request for technical comments. We incorporated agency comments into this report as appropriate.

We also offered experts who participated in our work the opportunity to review and comment on a draft of this report. We received technical comments from 14 experts and incorporated them as appropriate.

We are sending copies of this report to the appropriate congressional committees and other interested parties. In addition, the report is available at no charge on the GAO website at http://www.gao.gov.

If you or your staff members have any questions about this report, please contact Karen L. Howard, PhD at HowardK@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix III.

//SIGNED//

Karen L. Howard, PhD

Director,

Science, Technology Assessment, and Analytics

Appendix I: Objectives, Scope, and Methodology

Objectives

We describe our scope and methodology for addressing the three objectives outlined below:

1. What are current and emerging organ-on-a-chip (OOC) technologies, and what are their benefits?
2. What are the challenges to developing and using these technologies?
3. What options could policymakers consider to help enhance the benefits or mitigate the challenges?

To address all research objectives, we conducted a literature search, reviewed key reports and peer-reviewed articles, and convened a 2-day expert discussion group. In addition, we interviewed a selection of key experts, including those from federal agencies; academia; nonprofits; and private companies, including developers and end users of OOCs. We also attended 3 technical conferences or workshops and visited labs researching OOC and cell-based systems at the National Institute of Standards and Technology (NIST) to better understand these technologies.

Scope

The scope of our assessment included OOCs that are currently in use or in development by academic, industrial, or government researchers. For the purposes of this report, we define OOCs to be small, experimental laboratory tools that contain human cells and mimic how organs and systems in the human body work. This includes both tools that include a microfluidic component (i.e., media flowing through small channels in a 3D system), as well as other cell-based tools such as organoids (i.e., small, artificially grown groups of human cells). We did not include other advanced tools such as 3-dimensional bioprinted tissues and organs. The OOCs described in this report are illustrative examples of the range of applications of the technology and are not an exhaustive list. We assessed the general status of OOC to model various organs but did not assess the product of any particular developer.

Methodology

Literature search and review

For all objectives, we reviewed relevant literature identified by agency officials, experts, and our literature search. A GAO research librarian conducted a literature search to identify articles relevant to all objectives. The librarian searched a variety of databases, including through ProQuest (e.g., Chemical Engineering & Biotechnology Abstracts, Lancet Title, ProQuest Biological & Health Science Professional) and SCOPUS, using terms such as organ-on-a-chip, research and development, and benchmark. We narrowed our search to articles published in the last 5 years to capture recent development and uses of OOCs.[42] Results of

[42]Some articles identified during the course of our work were published before this date.

these searches could include scholarly or peer-reviewed material; government reports; trade or industry papers; association, nonprofit, and think tank publications; or legislative materials. The search results yielded 425 articles for initial selection and review. We selected 82 articles most relevant to our objectives for further review. We gathered additional information using a snowball technique.[43]

Interviews

We interviewed a selection of agency officials and experts with experience and perspectives on the above objectives. (See app. II for a list of experts we spoke with.) We identified these interviewees from our review of the literature, the conferences we attended, and other interviews. We ensured that interviewees represented a diversity of views by selecting individuals or organizations from multiple sectors (e.g., government, industry), OOC applications (e.g., pharmaceutical, agrochemical), and roles (e.g., OOC developer, end user, regulator). Interviewees included officials or representatives from

- four relevant federal agencies—the U.S. Environmental Protection Agency, including the Office of Research and Development and Office of Chemical Safety and Pollution Prevention; the U.S. Department of Health and Human Services, including the National Institutes of Health and the Food and Drug Administration; the U.S. Department of Commerce, including the National Institute of Standards and Technology; and the U.S. Department of Defense, including the Defense Threat Reduction Agency;
- one European government agency that regulates drugs;
- five academic researchers or research groups;
- six private companies including both OOC developers and end users for different applications (e.g., pharmaceutical, agrochemical);
- two industry consortia; and
- two nonprofits.

Because this is a purposeful, nongeneralizable selection of the stakeholders involved in developing and using OOCs, the results of our interviews are illustrative and are not generalizable to all expert perspectives.

Expert discussion group

We convened an expert discussion group to inform our assessment of OOC technologies. The meeting was held virtually over 2 days with a total of 16 experts.[44] (See app. II for a list of experts we spoke with, including discussion group participants.) We identified subject matter experts covering significant areas of our assessment—including OOC developers, end users, research funders, and those with relevant expertise such as toxicology or policy—based on information from our interviews, our review of literature and other documentation, the conferences

[43]The snowball technique involves identifying additional articles or reports within those we had already reviewed on the topic.

[44]Some experts were only able to attend one of the two days. 10 experts participated on the first day; 13 experts participated on the second day; and 7 experts participated on both days.

we attended, and web searches (e.g., conference and industry websites). We interviewed a selection of these subject matter experts to better understand various perspectives on OOC technology as described above. Of the interviewees, we selected 12 experts to participate in the discussion group. We selected an additional 4 experts based on expert recommendations and their specific area of expertise. Experts were selected considering a balance of perspectives from a variety of sectors (federal government; academia; industry; and nonprofits). From these sectors, we included experts who research and develop OOCs (developers), experts who use OOCs (end users), and experts who do both. We also included those with other expertise, such as policy expertise relevant to OOCs.

We evaluated the experts for potential conflicts of interest, which we considered to be any current financial or other interest that might conflict with the service of an individual because it could (1) impair objectivity or (2) create an unfair competitive advantage for any person or organization. We determined 14 experts to be free of reported conflicts of interest. Two experts reported conflicts of interest, which we determined to be outside the scope of the meeting or sufficiently addressed by the overall design of our meeting and methodology because discussions did not revolve around any specific technology, company, or vested interest. The 16 experts collectively were determined to not have any inappropriate biases. The comments of experts represented their individual views and not the organizations with which they were affiliated and are not generalizable to the views of others in the field.

We divided the 2-day discussion group into three moderated discussion sessions: (1) state of OOC technologies, including potential benefits and developmental status; (2) challenges to developing and using OOCs; and (3) potential policy options. We provided discussion questions and prompts for each session and invited all experts to participate in the discussion. The meeting was professionally transcribed to ensure that we accurately captured the experts' statements. After the meeting, we reviewed the transcripts to synthesize the responses and to inform our understanding of all three researchable objectives. We offered the experts at our discussion group the opportunity to review and provide technical comments on a draft of our report, which we incorporated as appropriate.

Policy options

Based on our research, we developed a series of policy options. Policy options are intended to represent possible actions that policymakers could take to address a policy objective. These options are not listed in any particular order, nor are they inclusive of all possible policy options. We consider policymakers to include legislative bodies, government agencies, academics, OOC developers, end users, and other groups. For each policy option, we discussed potential opportunities and considerations. We limited policy options to those that fit the objective and fell within the report scope.

We developed six policy options that could help enhance the benefits or address the challenges to development and use of OOCs, including maintaining the status quo (i.e., taking no action beyond activities that are already occurring). For each policy option, we

identified multiple implementation approaches that policymakers could consider. To develop these, we compiled a list of possible approaches over the course of our work based on interviews, our expert discussion group, and literature. We further refined and assessed these approaches to ensure they were adequately supported by the evidence we collected and fit into the overall scope of our work. We then analyzed the information we collected to identify potential opportunities and considerations of each approach. We did not conduct work to assess how effective the options may be and express no view regarding the extent to which legal changes would be needed to implement them. The policy options, implementation approaches, and analyses were supported by documentary and testimonial evidence.

We conducted our work from January 2024 to May 2025 in accordance with all sections of GAO's Quality Assurance Framework that are relevant to technology assessments. The framework requires that we plan and perform the engagement to obtain sufficient and appropriate evidence to meet our stated objectives and to discuss any limitations to our work. We believe that the information and data obtained, and the analysis conducted, provide a reasonable basis for any findings and conclusions in this product.

Appendix II: Expert Participation

To conduct our work, we interviewed experts with experience as developers, end users, funders, or regulators of organ-on-a-chip technologies. We also convened an expert discussion group, which was held virtually over 2 days in September 2024. Experts who participated in these interviews or discussions are listed below. Some of these experts provided additional assistance throughout our work, including sending materials for review. In addition, 11 experts provided feedback on policy options early in the drafting process. Fourteen experts reviewed our draft report for accuracy and we incorporated their technical comments as appropriate.

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Appendix III: GAO Contact and Staff Acknowledgments

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Staff acknowledgments

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