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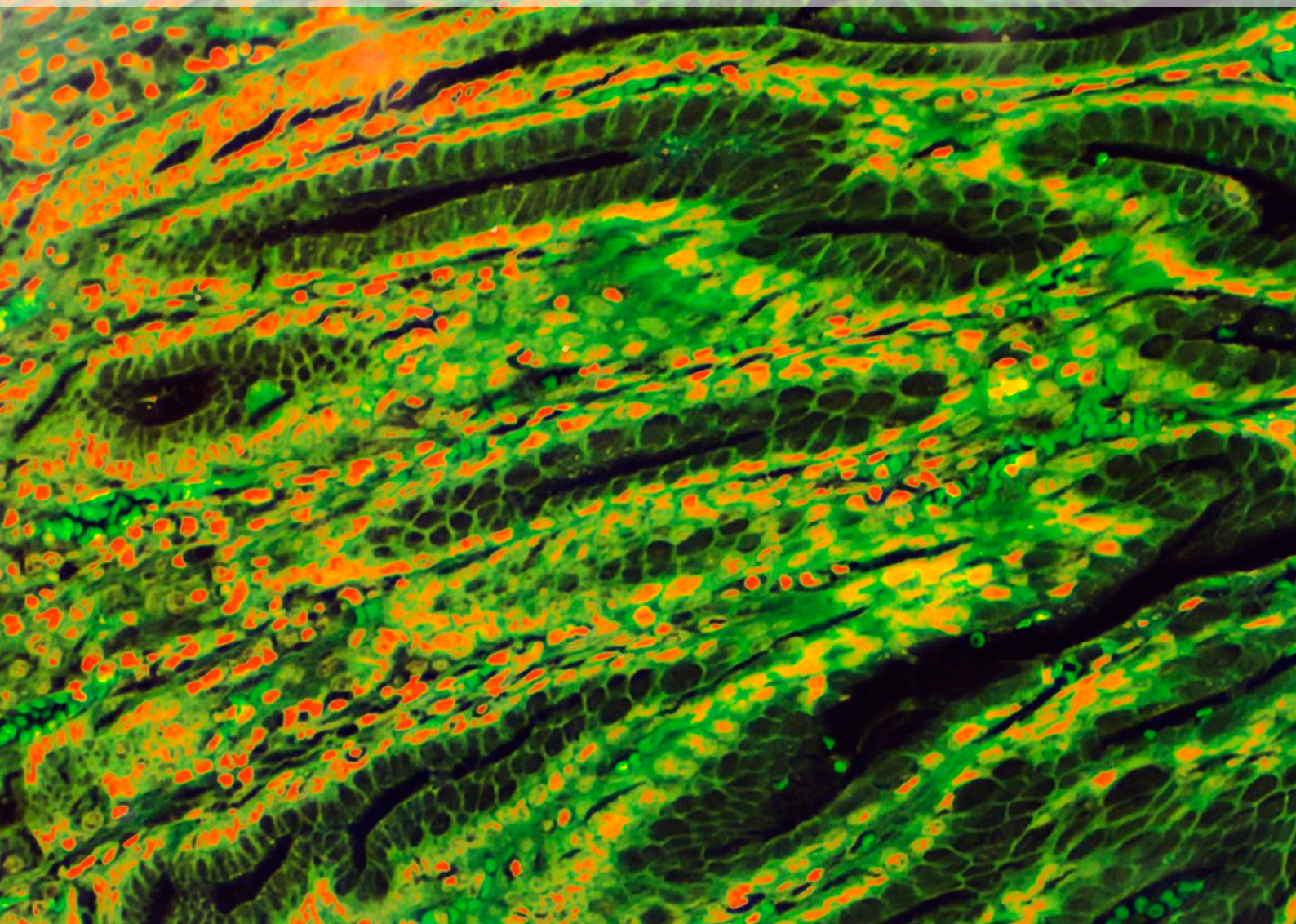
Non-animal models

A strategy for maturing Australia's medical product development capabilities

2023



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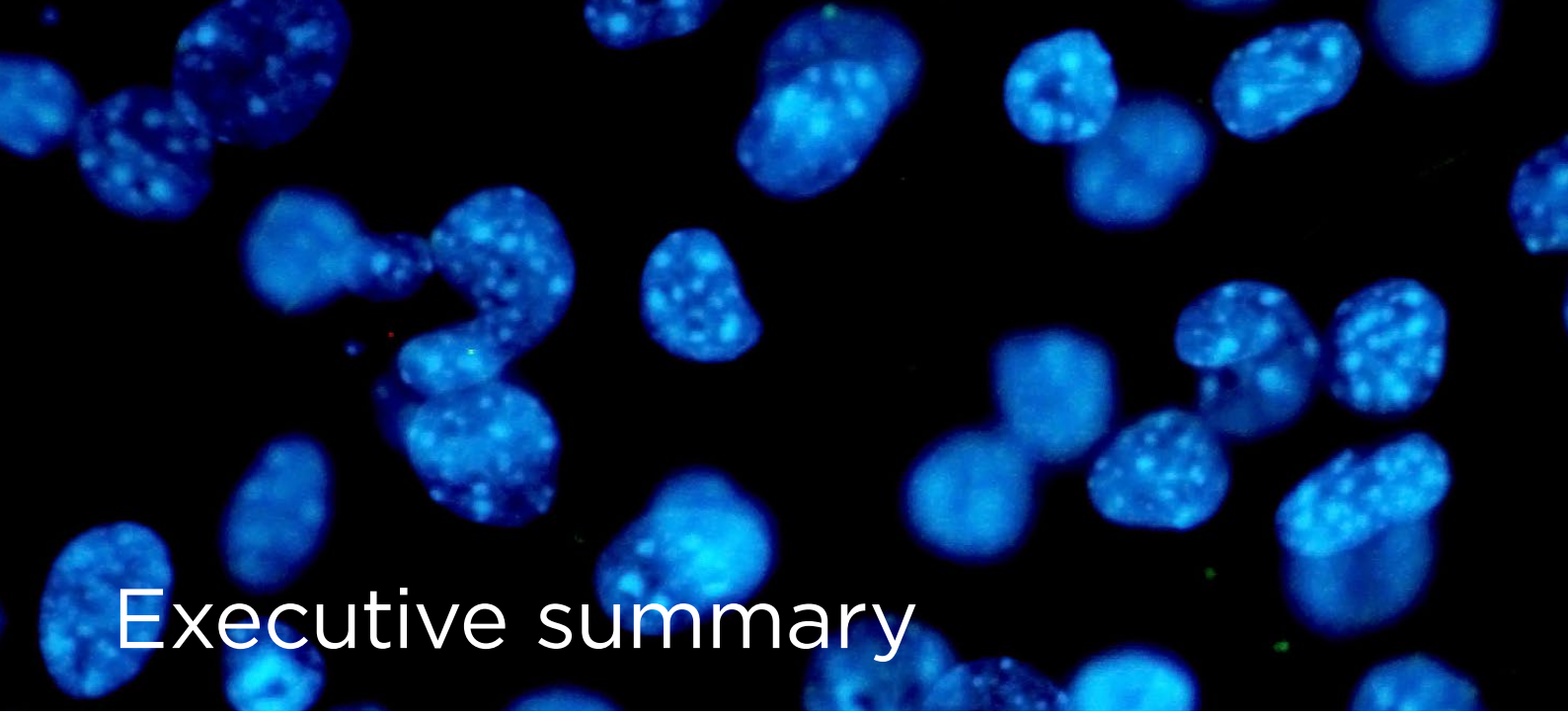


Executive summary

This report assesses the potential of emerging non-animal models to complement or replace traditional approaches in medical product development over the next 15 years. The analysis includes specific opportunities and recommendations for Australia to strategically enhance capability in this field, improve research quality and productivity, strengthen sovereign capability, and generate new national revenue streams.

The report defines non-animal models as biological models that use human-derived or humanised cells, tissues or data. While the scope of this analysis is restricted to non-animal model applications across the medical product development process, the report's recommendations could benefit applications in other fields, such as veterinary and agricultural medicines, cosmetic testing, and eco-toxicology.

The report was informed by consultation with **103** individuals from **66** organisations across industry, research and government.

Why non-animal models?

The complexity of non-animal models is rapidly increasing, equating to or surpassing the performance of traditionally used animal models in several applications. Due to their enhanced biological relevance, non-animal models can increase productivity and reduce costs by identifying unsuitable medical products earlier in development and re-investing savings in more promising candidates. These models also support broader global '3Rs' objectives to replace, reduce and refine the use of animals for research and testing purposes.

Why now?

Recent policy shifts in the United States and Europe encourage the transition away from animal use. These shifts are likely to support the already strong growth in the global non-animal testing market, valued at USD 1.11 billion in 2019, and expected to grow at a compound annual growth rate of 10.4% during 2019–2025. At the same time, animal model supply chains face increased risks, prompting alternative approaches to become more valuable.

Why Australia?

Australia has comparative global strengths in non-animal models for several organ systems likely to disrupt the status quo about the use of animal models over the next 15 years, including cardiovascular, respiratory, and nervous systems. Australia also possesses key foundational capabilities, including existing infrastructure (the National Collaborative Research Infrastructure Strategy – NCRIS – network), high throughput screening capabilities, and internationally recognised capacity for induced pluripotent stem cell generation, a key input for non-animal model development. These emerging models will also be critical to protect and further strengthen Australia's $1.4 billion clinical trials sector.

Australia must act now to secure a key role in this emerging capability.

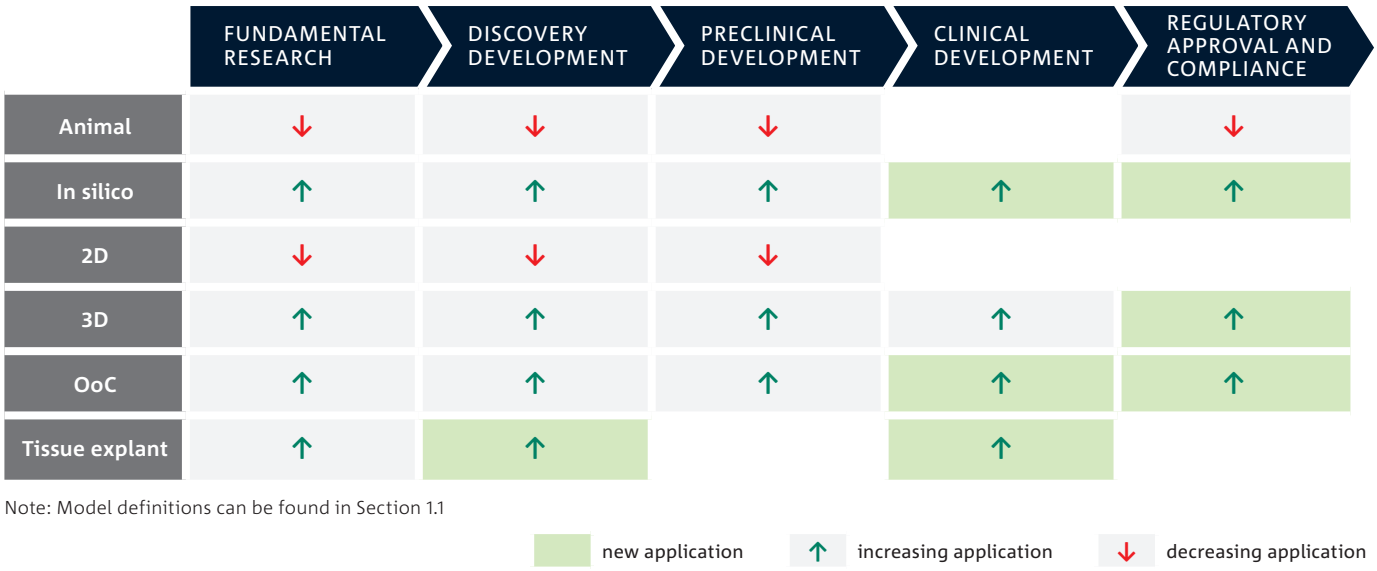
Despite relevant research and infrastructure strengths, Australia is still maturing and coordinating these national capabilities. This report seeks to support these coordination efforts. It discusses how Australia can accelerate non-animal model applications' demonstration, scaling, and commercial success.

The next 15 years will see an increase in the use of non-animal models across all stages of the medical product development process.

The most significant growth is likely to come from complex in vitro models such as organoids (3D) (estimated **$1.28 billion in revenue** for Australia by 2040) and organ-on-chip (OoC) technologies (**$310 million in revenue**).[1] In silico models are also anticipated to be more widely applied throughout the development process; used in conjunction with in vitro models to complement and validate findings. Figure 1 summarises the expected shifts in non-animal model use across stages of the medical product development process.

The organ systems most likely to see non-animal models replace the status quo include cardiovascular, respiratory, gastrointestinal, skin, eye, and liver.

Figure 1. Expected shifts in the use of models for medical product development



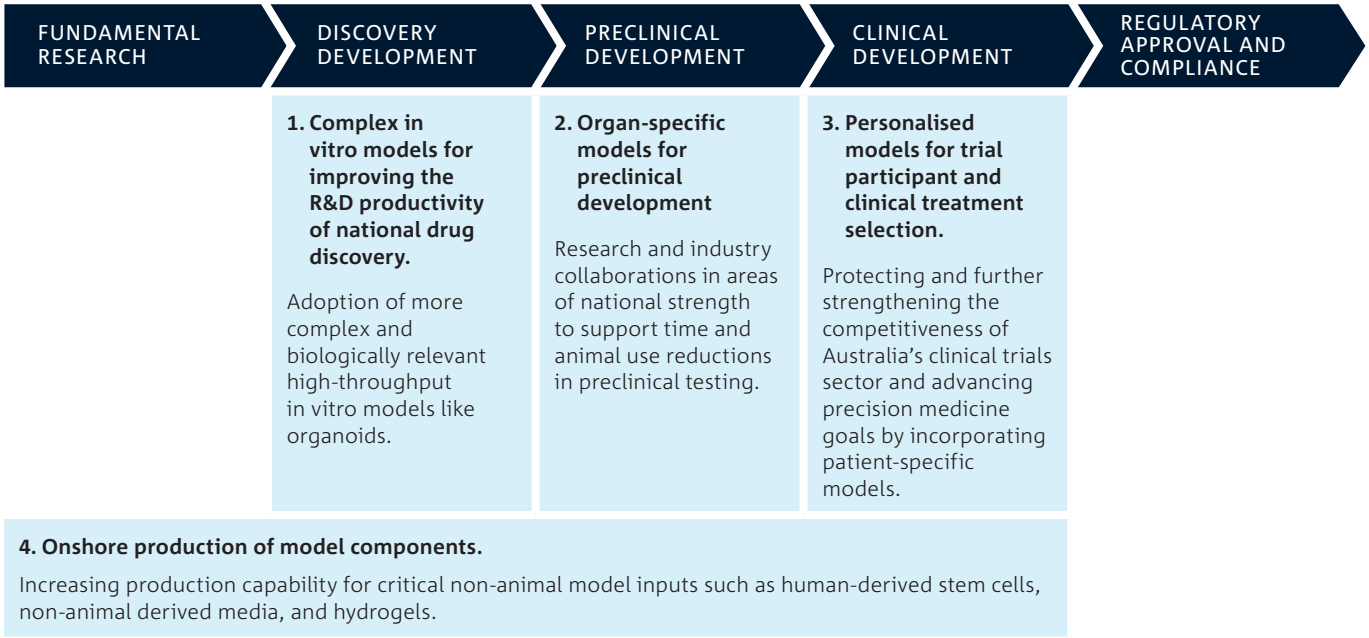
Note: Model definitions can be found in Section 1.1

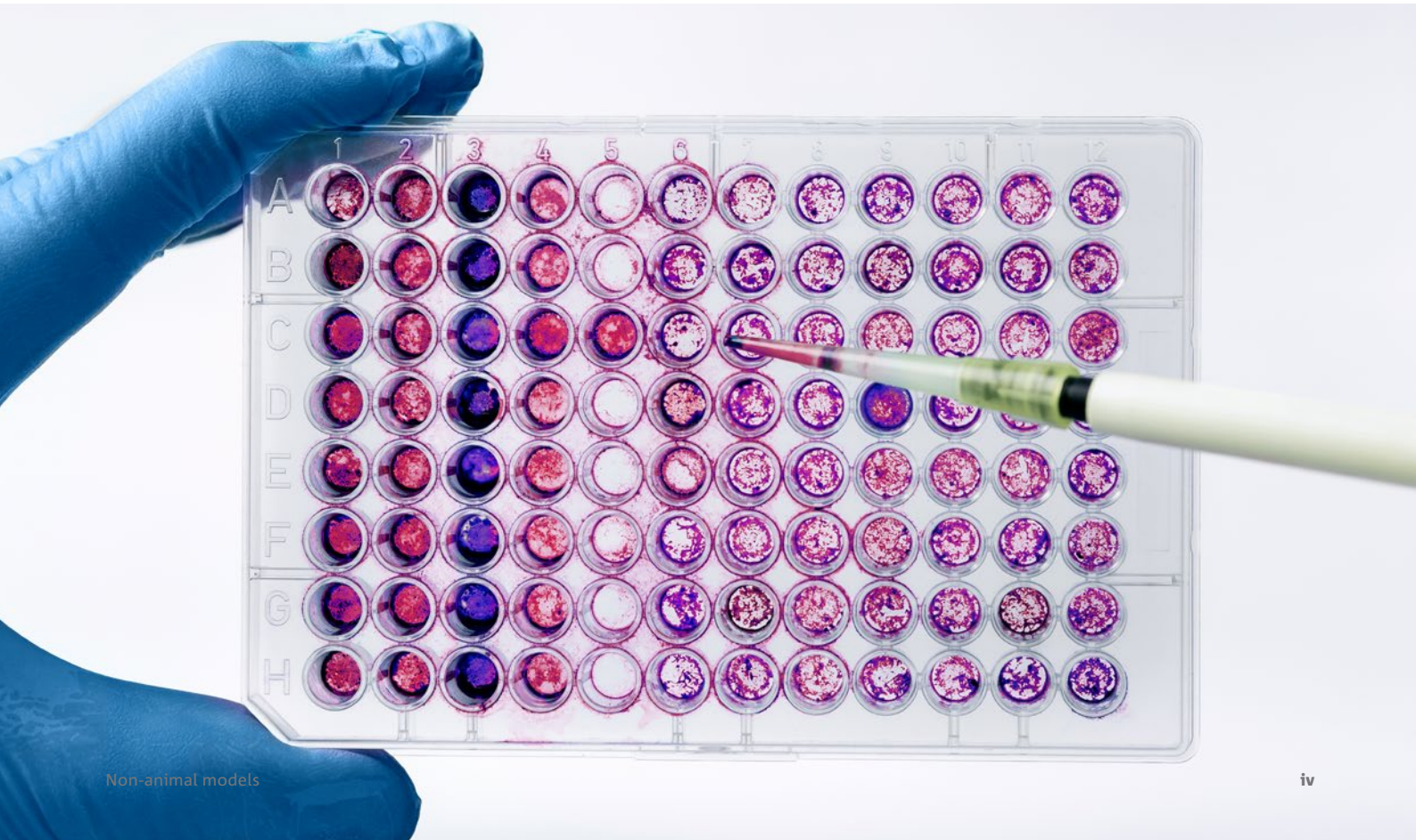
1 Based on CSIRO Futures economic analysis of global non-animal model market size data, Australian share of global publications by model and national wage data. See Appendix A.5 for the methodology used.

Four national opportunities pair Australian strengths with global needs.

Developing and applying non-animal models within these settings (Figure 2) can benefit the quality of domestic research and development (R&D) activities or create revenue streams for non-animal model applications by providing global services and partnerships.

Figure 2. Four national opportunities





Ten recommendations to provide Australia with the foundation to pursue these opportunities.

While the opportunities were developed considering a 15-year time horizon, setting Australia on a path towards these opportunities would require actioning the recommendations within five years. Within these five years, recommendations can be grouped and ordered by themes, with those aimed at coordinating and updating existing processes considered the most important first steps by those consulted (Figure 3). These activities would set a strong foundation for the remaining recommendations, which aim to integrate local capabilities into medical product development before strengthening production and commercialisation. Recommendations for non-animal model validation data will provide the evidence base to generate momentum across all themes. More discrete R&D priorities, actioned in parallel to recommendations, will act as supporting cross-cutting activities to strengthen Australia's non-animal models' capabilities further.

Figure 3. Recommendations and R&D priorities

Coordinate and update existing processes

1. Establish a national consortium that coordinates and promotes Australia's non-animal model capabilities
2. Develop national data collection standards on the use of animals in scientific research, teaching and testing
3. Align TGA processes and industry guidance with new FDA procedures for accepting non-animal model data

Integrate local capabilities

4. Develop a national biobanking and tissue collection network
5. Integrate outputs from NCRIS platforms into a coordinated pipeline for non-animal models

Strengthen production and commercialisation

6. Facilitate IP management and material access for research and industry collaborations
7. Enhance commercial skillsets across the non-animal model sector
8. Update biomedical R&D infrastructure to support non-animal model capabilities

Validation data

9. Conduct retrospective studies that compare animal and non-animal model predictivity
10. Conduct systematic reviews of locally and internationally developed non-animal models

R&D priorities

- Support the economic case for non-animal models in medical product development
- Improve analytics for increasingly complex in vitro models
- Advance the quality of model inputs and hardware
- Extend the capabilities of in vitro models for a closer recreation of human physiology across healthy and diseased states

Glossary

TERM	DEFINITION
3Rs	Framework for the ethical use of animals for scientific purposes centred on three principles:[2] *Replacement* is when non-animal alternatives can fully accomplish a project or process goal without animals. *Reduction* is when using fewer animals can accomplish the same goals, or increased information can be derived from the same number of animals. *Refinement* is when changes, practices or adaptations in a project or process can minimise the pain and distress of the animals used and enhance their well-being.
Biobank	Collection of biological specimens (cells, tissues, derivative models, blood, bodily fluids, or genetic material, most commonly of human origin) and related donor information (demographic background, medically relevant history, and clinical data) established and made available to support research activities.
Biological models	Any form of investigation that attempts to replicate animal physiology (including humans).
High-throughput screening (HTS)	Simultaneous, automated testing of large compound or gene-targeting libraries in simplified in vitro settings to identify a subset (hits) exhibiting a desired physical, chemical, or biological activity. HTS is the gold standard for small molecule and compound screening, through which approximately 100,000 drug-like molecules can be tested against a target per day to observe reactions and identify hits.
Humanised cells	Cells initially derived from an animal modified to resemble human counterparts regarding genetic information, expression profiles, metabolic networks, or overall behaviour.
Induced pluripotent stem cells (iPSCs)	Cells with morphology and behaviour resembling that of embryonic stem cells and capable of differentiation into most mature cell subtypes. These cells are used widely for disease modelling, regenerative medicine research, and drug discovery.
In silico	Category of models that use computational settings to simulate biological systems and their responses to an intervention.
In vitro	Category of models using biological components in manufactured, controlled settings (e.g., a culture flask) that are exterior to the organism(s) from which the components are derived.
In vitro to in vivo extrapolation (IVIVE)	In silico approach that scales up results obtained in vitro to anticipate a medical product's behaviour at the organ or whole-organism level (e.g., pharmacokinetics/dynamics) and to calculate exposure levels associated with an effect (e.g., dosimetry).[3]
Non-animal model	A subset of biological models that use human-derived or humanised cells, tissues, or data.
Omics	Grouping term encompassing studies, technologies and data associated with genomics, epigenomics, transcriptomics, proteomics, metabolomics, and lipidomics.
Precision medicine (or personalised medicine)	An approach to designing medical care that optimises efficiency and therapeutic benefit for individual patients or patient groups, by using omics and molecular profiling to predict response and guide clinical decision-making.
Quantitative systems pharmacology (QSP)	In silico approach that models medical product behaviour in an organism by linking together molecular and cellular mechanisms, product characteristics, and whole-organism dynamics.
Health digital twin	A computational model of a tissue, organ or entire system that mirrors the physical counterpart found within a patient. The models draw information from real-time sources, medical history, and population-wide assessments to model personalised health outcomes and support clinical decision-making.[4]

2 National Health and Medical Research Council (2019) Information paper: The implementation of the 3Rs in Australia. NHMRC, Canberra, Australia.

3 Chang X, Tan Y-M, Allen DG, Bell S, Brown PC, Browning L, Ceger P, Gearhart J, Hakkinen PJ, Kabadi SV, Kleinstreuer NC, Lumen A, Matheson J, Paini A, Pangburn HA, Petersen EJ, Reinke EN, Ribeiro AJS, Sipes N, Sweeney LM, Wambaugh JF, Wange R, Wetmore BA, Mumtaz M (2022) IVIVE: Facilitating the Use of In Vitro Toxicity Data in Risk Assessment and Decision Making. Toxics 10(5), 232.

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Contents

1 Introduction

1.1 What are non-animal models?

All medical products require research and testing to determine their safety and efficacy before human use.[5] These activities are done in biological models, with most performed in live animals (animal models). Non-animal models are a subset of biological models that use human-derived or humanised cells, tissues or data (Table 1). Key differences across existing non-animal model types include their ability to mimic tissue features, the spatial layout of cells, and the use of controllable biophysical stimuli. Appendix A.2 outlines further comparisons across non-animal model types.

1.2 Why non-animal models?

The 3Rs, principles of replacing, reducing and refining the use of animals in research, have been a fundamental ethical-research framework since the 1960s.[8] While the use of live animals in medical research will continue to be an important part of the medical product development process for the foreseeable future, the Australian code for the care and use of animals for scientific purposes requires the application of the 3Rs at all stages of animal care and use.[9]

Table 1. Non-animal model types

NON-ANIMAL MODEL		DEFINITION
In silico		Computational modelling or simulation of biological systems and their responses to an intervention.[6]
In vitro	2D	Cells cultured over a flat surface (well, culture plate or flask).
	3D	Cell cultures that interact with an externally provided 3D environment (scaffold) or self-assemble into 3D structures (spheroids and organoids), enabling cell migration and interaction.
	Organ-on-chip (OoC)	Culture in miniature engineered settings (chips) where the location of cells, the physical stimuli delivered to them (e.g., stretching), and a controllable flow mimic the characteristics of a tissue, organ or system.[7]
	Tissue explant	Small, dissected fragments of primary tissue that preserve features like cell diversity and microenvironment architecture (e.g., tissue biopsies).

5 Medical products are small molecules and biologicals that can be used to detect or treat disease, including diagnostics, therapeutic products, vaccines, and medical devices.

6 Piñero J, Furlong LI, Sanz F (2018) In silico models in drug development: where we are. Current Opinion in Pharmacology 42, 111–121.

7 Leung CM, Haan P de, Ronaldson-Bouchard K, Kim G-A, Ko J, Rho HS, Chen Z, Habibovic P, Jeon NL, Takayama S, Shuler ML, Vunjak-Novakovic G, Frey O, Verpoorte E, Toh Y-C (2022) A guide to the organ-on-a-chip. Nature Reviews Methods Primers 2(1), 33.

8 National Health and Medical Research Council (n.d.) The 3Rs. <https://www.nhmrc.gov.au/research-policy/ethics/animal-ethics/3rs> (accessed 10 July 2023).

9 National Health and Medical Research Council (2013) Australian code for the care and use of animals for scientific purposes, 8th edn, Commonwealth of Australia, Canberra, Australia. <https://www.nhmrc.gov.au/about-us/publications/australian-code-care-and-use-animals-scientific-purposes#toc__167> (accessed 10 July 2023).

In addition to ethical drivers for using alternatives to animal models, mature and emerging non-animal models possess a range of characteristics that can offer complementary benefits to animal models and, in time, may evolve to replace the use of animals in several research settings. These benefits include:

- **Enhanced biological relevance:** Several non-animal models offer the potential to better mimic human responses compared to animal models, and they can more accurately account for human population diversity, as they are derived from human cells.[10] Limitations of animal models include inter-species differences, inter-study variability, and low predictivity of toxicity in phase 1 clinical trials.[11] Whereas non-animal models have successfully predicted human clinical findings across toxicity, biomarker signals, and drug sensitivity.[12]
- **Cost savings and increased productivity:** Approximately 90% of medical products fail in clinical development (during phase I, II and III clinical trials) despite the use of animal tests, in large part due to efficacy or safety issues.[13] The use of more biologically relevant models may identify these issues earlier. These models may help products fail where necessary before human trials, which account for 69% of R&D costs in pharmaceutical development.[14] Earlier failure of unsuitable products can lower attrition rates during human trials and focus investment on promising candidates, directly impacting sector productivity. For example, an economic impact study estimated that widely adopting a single organ-on-chip for a single liver toxicity test could generate an additional USD 3 billion annually for the pharmaceutical sector.[15]
- **Alternative where animal model use is challenging:** Non-animal models can model rare diseases and disorders that would be costlier or more difficult to study through traditional approaches (animal models and clinical trials), due to statistical limitations and lower revenue potential of smaller patient populations.[16] Non-animal models can also be used for research and testing where the disease, condition, or toxicity of interest cannot be reliably induced in an animal.[17]
- **Applicable to high-throughput screening (HTS):** Some non-animal models have significant potential to interface with HTS. This approach is unsuitable for animal models due to the many compounds tested. Conservatively, HTS offers a 50- to 200-fold increase in testing efficiency compared to conventional in vitro 2D methods.[18] HTS allows for faster and potentially more cost-effective testing of multiple candidates and doses for medical product development and precision medicine.
- **Social license benefits:** As the social license for animal research and testing diminishes, the demand for products developed using alternatives will grow. Transitioning away from animal models may also increase employee satisfaction across the research community.

As emerging non-animal models continue advancing through validation processes, which require the support of animal models, the short to medium term will likely see non-animal models complement and rationalise animal model use rather than fully replace it.

10 Additional comparisons of biological resemblance, technological maturity and other considerations can be found in Appendix A.2.

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1.3 Why now?

The biological model landscape is changing rapidly, and several factors are driving an escalation in the pace of development and adoption of non-animal models, including:

- **Limited and vulnerable access to animals:** There are constraints on the availability of non-human primates for medical research due to increased demand from infectious disease research spurred by the COVID-19 pandemic, international transport issues, and limitations imposed by major suppliers in Asia.[19] There is a potential 5-year waiting list in Australia at the National Non-Human Primate Breeding and Research Facility, arising from the inherent difficulty in forecasting and matching future demand.[20] Mice, which comprise the majority of animals used for human or animal biology research purposes in Australia, also face local supply challenges, as demonstrated by the 2021 near closure of the Western Australia Animal Resources Centre.[21] Further, importing animal models not produced locally (e.g., guinea pigs and golden hamsters) involves a logistically demanding process with strict biosecurity regulations.[22]
- **International policy changes:** International policy, regulation and legislation changes encourage (and sometimes mandate) the development and adoption of non-animal models.[23] For example, European Union (EU) law requires non-animal models and approaches wherever possible, and the European Parliament has passed a resolution requesting an EU-wide action plan for ending animal model testing by 2030.[24] In the United States (US), the Environmental Protection Agency announced plans to eliminate requests for and funding of all mammalian studies by 2035.[25] Further, the US Congress passed the 'FDA Modernization Act 2.0' in 2022, modifying pre-existing language explicitly to allow the use of non-animal models to fulfil testing requirements.[26]
- **Global capability is rapidly maturing:** Leading jurisdictions, such as the US, EU, and the United Kingdom (UK),[27] have created non-animal model strategies and established institutions dedicated to supporting non-animal model development and validation. Examples include the US National Center for Advancing Translational Sciences (NCATS) and its Tissue Chip consortium, the UK National Centre for the Replacement Refinement and Reduction of Animals in Research (NC3Rs), the EU Organ-On-Chip Society (EUROoCs) and Reference Laboratory for alternatives to animal testing (EURL ECVAM), and the Netherlands Human Organ and Disease Model Technologies consortium (hDMT).

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25 US Environmental Protection Agency (2019) Administrator Wheeler Signs Memo to Reduce Animal Testing, Awards $4.25 Million to Advance Research on Alternative Methods to Animal Testing. <https://www.epa.gov/newsreleases/administrator-wheeler-signs-memo-reduce-animal-testing-awards-425-million-advance> (accessed 10 July 2023).

26 117th United States Congress (2022) FDA Modernization Act 2.0. <https://www.congress.gov/117/bills/s5002/BILLS-117s5002cps.pdf> (accessed 10 July 2023).

27 Interagency Coordinating Committee on the Validation of Alternative Methods (2018) A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States. National Toxicology Program (NTP).

- Leading jurisdictions are also establishing specific funding and translational projects for non-animal models, such as the NCATS' Tissue Chip for Drug Screening and past EU projects from Horizon 2020 like ORCHID,[28] OrganTrans,[29] and PATROLS.[30] In 2022 the US National Institutes of Health (NIH) provided USD 89 million to 214 organoid-related projects and USD 256 million to 608 organ-on-chip-related projects.[31] Similarly, the EU will contribute up to EUR 37 million of dedicated funding in 2024 for non-animal model research.[32]
- **Industry shifts:** Pharmaceutical companies are increasingly focusing on improved data collection and transparency around animal testing to drive innovation and advance the 3Rs.[33] Pharmaceutical companies are also leveraging non-animal models to support preclinical research and reduce the number of animals used, as demonstrated by Roche's investments in human-relevant models that have seen a 40% reduction in experimental animal use over the past ten years.[34]
- **Growing global market:** There is a growing international and domestic market of alternatives to animal testing.[35] The global non-animal testing market's value was USD 1.11 billion in 2019, and is expected to grow at a compound annual growth rate (CAGR) of 10.4% during 2019–2025.[36]

1.4 Why Australia?

Australia has comparative global strengths in various non-animal model applications (see Section 3). World-class Australian researchers across diverse organ systems support these. Australia also boasts a globally competitive clinical trials sector – valued at **$1.4 billion annually** – that can be protected and further strengthened by applying non-animal models.[37]

Building non-animal model capabilities can also provide flow-on benefits to other nationally important sectors (e.g., through applications in veterinary and agricultural medicines development), to valuable national environmental assets (e.g., through applications in eco-toxicology), and to ancillary technologies (e.g., microfabrication, data capture and analysis, and biological supplies).

Australia possesses a foundation of non-animal model-related expertise, academic output, and research infrastructure. However, it is yet to leverage these characteristics into a comprehensive national capability for medical product development. Through nationally coordinated investments into non-animal model capabilities, Australia can pursue the opportunities outlined in this report (Section 4.1) to improve domestic R&D and generate novel revenue streams by providing global services and partnerships.

28 Mastrangeli M, Millet S, Mummery C, Loskill P, Braeken D, Eberle W, Madalena C, Fernandez L, Graef M, Gidrol X, Picollet-D'Hahan N, van Meer B, Ochoa I, Schutte M, van den Eijnden-van Raaij J (2019) Organ-on-Chip In Development ORCHID Final Report. <https://h2020-orchid.eu/> (accessed 10 July 2023).

29 OrganTrans Consortium (2020) OrganTrans: Process for organoids transplantation. <https://organtrans.eu/#aboutproject> (accessed 10 July 2023).

30 PATROLS - Physiologically Anchored Tools for Realistic nanOmateriaL hazard aSsessment (2021) PATROLS: Advanced Tools for NanoSafety Testing. <https://www.patrols-h2020.eu/about-us/index.php> (accessed 10 July 2023).

31 United States National Institutes of Health (2023) Modernized NIH RePORTER version 2020.9 (02/04/2023 data). <https://reporter.nih.gov/> (accessed 2 April 2023).

32 European Commission - Single Electronic Data Interchange Area (SEDIA) (2023a) Gaining experience and confidence in New Approach Methodologies (NAM) for regulatory safety and efficacy testing – coordinated training and experience exchange for regulators, Funding & tender opportunities. <https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/horizon-hlth-2024-ind-06-09> (accessed 10 July 2023); European Commission - Single Electronic Data Interchange Area (SEDIA) (2023b) Innovative non-animal human-based tools and strategies for biomedical research, Funding & tender opportunities. <https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/horizon-hlth-2024-tool-05-06-two-stage;callCode=HORIZON-HLTH-2024-TOOL-05-two-stage> (accessed 10 July 2023).

33 Novartis (2023) Novartis in Society Integrated Report 2022. <https://www.novartis.com/sites/novartiscom/files/novartis-integrated-report-2022.pdf> (accessed 10 July 2023).

34 F. Hoffmann-La Roche (2023) Reducing animal testing, Animal Research at Roche. <https://live.roche.com/innovation/ethical-standards/animal-research/alternatives> (accessed 10 July 2023).

35 Vitika V, Surya N (2022) Non-Animal Alternative Testing Market, Allied Market Research. <https://www.alliedmarketresearch.com/non-animal-alternative-testing-market-A25675> (accessed 10 July 2023).

36 Global non-animal testing market includes academic research institutions and various industries (such as pharmaceuticals, medical devices, chemicals & pesticides and cosmetics) performing animal testing to conduct basic research, toxicology profiling, and others. The Business Research Company (2023) Global Animal Testing And Non-Animal Alternative Testing Market Report And Strategies To 2032. <https://www.thebusinessresearchcompany.com/report/animal-testing-and-non-animal-alternative-testing-market> (accessed 10 July 2023).

37 MTPConnect (2021) Australia's Clinical Trials Sector: Advancing innovative healthcare and powering economic growth. <https://www.mtpconnect.org.au/images/MTPConnect_Australia's%20Clinical%20Trials%20Sector%20report%202021.pdf> (accessed 10 July 2023).

2 Non-animal models in medical product development

2.1 Medical product development

Medical products must follow a development process before being approved for human use and commercialisation (Table 2). Each stage of development aims to advance the understanding of a product's interactions within the human body, refine its characteristics to maximise efficacy and minimise safety concerns. Product development does not necessarily follow a sequential path through these stages, as regulatory and validation requirements can vary by product type and jurisdiction. However, the progression through these stages relies on satisfying mandatory primary activities before advancing to human trials in clinical development.

Table 2. Medical product development stages

DEVELOPMENT STAGE	PURPOSE	PRIMARY ACTIVITIES
Fundamental research	Typically follows one of two objectives: • Understanding the mechanisms of organ and tissue function. • Modelling disease phenotypes to observe cell behaviour and interaction.	• Basic science • Disease modelling • Model development and validation
Discovery development	Selecting a potential medical product (candidate) for preclinical development.	• Target identification and validation • Compound screening and lead optimisation
Preclinical development	Determining the safety and efficacy of the medical product candidate prior to studies in humans.	• Safety – Pharmacodynamics, pharmacokinetics, and toxicology • Efficacy – Biopharmaceutics and clinical efficacy-supporting studies
Clinical development	Evaluating the efficacy of new medical products and the application of novel clinical techniques directly in humans.	• Clinical trials – Phase I–III • Clinical applications, e.g., precision medicine
Regulatory approval and compliance	Obtaining approval before initiating human studies in clinical development, when progressing through phases of clinical trials, and when obtaining marketing authorisation prior to commercialisation.	Approval • Safety assessments of complex or novel therapeutic goods • Validation and qualification of models for specific contexts of use Compliance • Batch release testing for well-known pharmaceutical ingredients • Categorisation of hazards for product labelling of well-established and low-complexity therapeutic goods

2.2 Current non-animal model use

A range of non-animal models are currently used in medical product development. However, the application of specific types varies by development stage. Investigation of all non-animal model types for their potential use in medical product development is underway; however, the inclusion of a model type in the current state analysis was determined by whether the model type is already used by the industry for internal decision-making or in the regulatory approval of a novel medical product (see Figure 4).

Fundamental research

Animals are the most common biological model used for fundamental research. The latest comparable Australian State and Territory data indicates that the use of animals for 'understanding human or animal biology' accounted for 20.2% of all reported research and teaching uses in Victoria in 2020, 12.1% in New South Wales in 2020, and 12.6% in Tasmania in 2021.[38]

In vitro 2D is the most common non-animal model type used in fundamental research, providing insight into cell behaviour, gene activity and response to external compounds for many diseases. For instance, the Cancer Cell Line Encyclopedia was a project that performed an extensive pharmacological profiling of cancer cell lines using the traditional 2D culture setting.[39] In recent years, in silico and more complex in vitro models (3D, organ-on-chip and tissue explants) are becoming increasingly common in fundamental research, both in replacing animal models and providing new sources of insight.[40]

Figure 4. Current models used for medical product development

FUNDAMENTAL RESEARCH	DISCOVERY DEVELOPMENT	PRECLINICAL DEVELOPMENT	CLINICAL DEVELOPMENT	REGULATORY APPROVAL AND COMPLIANCE
Animal	Animal	Animal		Animal
In silico	In silico	In silico		
2D	2D	2D		
3D	3D	3D	3D	
OoC	OoC	OoC		
Tissue explant				

38 Animal Welfare Victoria (2022) Statistics of animal use in research and teaching, Victoria: 1 January 2020 – 31 December 2020, Department of Jobs, Precincts and Regions, Melbourne, Australia. <https://agriculture.vic.gov.au/__data/assets/pdf_file/0009/880047/2020-Statistics-of-animal-use-in-research-and-teaching-report_FINAL.pdf> (accessed 10 July 2023); Department of Natural Resources and Environment Tasmania (2022) Animal Research Statistics Tasmania: Annual Report. State of Tasmania, Hobart, Australia. <https://nre.tas.gov.au/Documents/Animal%20Research%20Report%20Number%2026%20for%202021.pdf> (accessed 10 July 2023); NSW Government Department of Primary Industries (2021) NSW 2020 Animal Use in Research Statistics. NSW Government, Sydney, Australia. <https://www.animalethics.org.au/__data/assets/pdf_file/0007/1395466/INT21-148540-2020-Animal-use-in-research-statistics-report.pdf> (accessed 10 July 2023); Turner L (2021) DAF Animal Ethics Committees Annual Report Summary for the period 1 July 2020 to 30 June 2021. State of Queensland, Brisbane, Australia. <https://www.publications.qld.gov.au/ckan-publications-attachments-prod/resources/fa04f14f-f5b3-48bc-a7ca-136e93b69961/summary-2020-21-aec-annual-report.pdf?ETag=07b43ba4a0e56f916a5f99c147747aa8> (accessed 10 July 2023).

39 Broad Institute (n.d.) Cancer Cell Line Encyclopedia (CCLE). <https://sites.broadinstitute.org/ccle/> (accessed 11 July 2023).

40 Blinova K, Dang Q, Millard D, Smith G, Pierson J, Guo L, Brock M, Lu HR, Kraushaar U, Zeng H, Shi H, Zhang X, Sawada K, Osada T, Kanda Y, Sekino Y, Pang L, Feaster TK, Kettenhofen R, Stockbridge N, Strauss DG, Gintant G (2018) International Multisite Study of Human-Induced Pluripotent Stem Cell-Derived Cardiomyocytes for Drug Proarrhythmic Potential Assessment. Cell Reports 24(13), 3582–3592; Cimen Bozkus C, Bhardwaj N (2021) Tumor organoid-originated biomarkers predict immune response to PD-1 blockade. Cancer Cell 39(9), 1187–1189; Lawrence CL, Pollard CE, Hammond TG, Valentin J-P (2008) In vitro models of proarrhythmia. British Journal of Pharmacology 154(7), 1516–1522.

Discovery development

Target identification uses in vitro 2D models due to the large number of compounds and experimental conditions to evaluate, as well as the high reproducibility required. On the other hand, target validation studies use animal models (mainly mice) due to their physiological complexity, lower cost, short lifespan, and relative ease of breeding.

Target identification and validation activities are sometimes complemented by in silico models or complex in vitro models such as organoids or organs-on-chips. In silico models can incorporate and analyse primary data to identify, and at times even select and prioritise, potential targets.[41] At the same time, organoid and organ-on-chip models pose value due to their higher complexity across cellular interaction and structure, increased biological relevance, and their amenability to genetic modification.[42] The increasingly complementary role of non-animal models stems from limitations of disease modelling using animals. For instance, mice are often used as genetic disease models in screenings to validate identified therapeutic targets.[43] However, they can be inaccurate in fully recreating disease hallmarks. This is the case for Alzheimer's disease (AD), with a complex 'brain in a dish' organoid model more closely demonstrating anatomical and physiological properties of AD-impacted human brain tissue.[44]

As with target identification, compound screening activities require models that can be used at high speeds with minimal variation (i.e., highly reproducible) and so are commonly performed using in vitro 2D models. In recent years higher complexity in vitro 3D models have also been used for compound screening when a lower throughput is acceptable, as they can be more representative of human physiology and potentially more accurate in predicting responses.

Lead optimisation, which involves making chemical modifications to the most promising molecules' characteristics (i.e., their structure) to generate refined drug-like compounds, is informed by both in vitro and in silico models.

Preclinical development

While a large amount of preclinical data is generated using simple, lower-cost in vitro 2D models, many pharmacology studies in preclinical development require disease-specific and physiologically complex models to gain a more accurate insight into systemic effects. In these cases, animal models are commonly used alongside in silico models, such as quantitative systems pharmacology (QSP) and physiologically based pharmacokinetic (PBPK) models. In support of the transition away from animal use in pharmacology studies, the US Food and Drug Administration (FDA) has waived the requirement for clinical drug-drug interaction studies in animal models where in vitro tests have demonstrated strong in vitro-in vivo human correlation and validated their human concordance.[45]

Preclinical toxicology studies are highly organ-specific, and regulators often require these studies in two animal models (a rodent and a non-rodent species), complemented by in vitro 2D models. However, more complex in vitro models (i.e., organoids and organs-on-chips) and in silico models have begun to demonstrate higher accuracy in assessing organ-specific toxicology.[46] As an illustration, Emulate (US), a spin-out from Harvard University, produces organ-on-chip models across multiple preclinical applications and organs.[47] In 2019, their liver-chip model demonstrated a more accurate prediction of human toxicity than animal model equivalents, sometimes flagging compounds that animal models missed.[48]

41 Agamah FE, Mazandu GK, Hassan R, Bope CD, Thomford NE, Ghansah A, Chimusa ER (2020) Computational/in silico methods in drug target and lead prediction. Briefings in Bioinformatics 21(5), 1663–1675.

42 Shamshirgaran Y, Jonebring A, Svensson A, Leefa I, Bohlooly-Y M, Firth M, Woollard KJ, Hofherr A, Rogers IM, Hicks R (2021) Rapid target validation in a Cas9-inducible hiPSC derived kidney model. Scientific Reports 11(1), 16532.

43 Buchovecky CM, Turley SD, Brown HM, Kyle SM, McDonald JG, Liu B, Pieper AA, Huang W, Katz DM, Russell DW, Shendure J, Justice MJ (2013) A suppressor screen in Mecp2 mutant mice implicates cholesterol metabolism in Rett syndrome. Nature Genetics 45(9), 1013–1020; Landrette SF, Xu T (2011) Somatic Genetics Empowers the Mouse for Modeling and Interrogating Developmental and Disease Processes. PLoS Genetics 7(7), e1002110.

44 Blanchard JW, Victor MB, Tsai L-H (2022) Dissecting the complexities of Alzheimer disease with in vitro models of the human brain. Nature Reviews Neurology 18(1), 25–39.

45 Zhang D, Luo G, Ding X, Lu C (2012) Preclinical experimental models of drug metabolism and disposition in drug discovery and development. Acta Pharmaceutica Sinica B 2(6), 549–561.

46 Jean D, Naik K, Milligan L, Hall S, Mei Huang S, Isoherranen N, Kuemmel C, Seo P, Tegenge MA, Wang Y, Yang Y, Zhang X, Zhao L, Zhao P, Benjamin J, Bergman K, Grillo J, Madabushi R, Wu F, Zhu H, Zineh I (2021) Development of best practices in physiologically based pharmacokinetic modeling to support clinical pharmacology regulatory decision-making—A workshop summary. CPT: Pharmacometrics & Systems Pharmacology 10(11), 1271–1275; Matsui T, Shinozawa T (2021) Human Organoids for Predictive Toxicology Research and Drug Development. Frontiers in Genetics 12, 767621.

47 Emulate (n.d.) About Us – A Culture of Innovation. <https://emulatebio.com/about/> (accessed 11 July 2023).

48 Jang K-J, Otieno MA, Ronxhi J, Lim H-K, Ewart L, Kodella KR, Petropolis DB, Kulkarni G, Rubins JE, Conegliano D, Nawroth J, Simic D, Lam W, Singer M, Barale E, Singh B, Sonee M, Streeter AJ, Manthey C, Jones B, Srivastava A, Andersson LC, Williams D, Park H, Barrile R, Sliz J, Herland A, Haney S, Karalis K, Ingber DE, Hamilton GA (2019) Reproducing human and cross-species drug toxicities using a Liver-Chip. Science Translational Medicine 11(517), eaax5516.

Clinical development

While clinical development involves trialling medical products directly in humans, the use of organoids supports personalised medicine in clinical settings and can help investigate the mechanisms of action behind unexpected responses.[49] These patient-specific models can predict an individual's response to an already approved medical product without bearing the risk of an adverse reaction or treatment resistance. For example, intestinal organoid models have successfully been used in the Netherlands for several years to inform therapeutic regimens for cystic fibrosis patients.[50] Similarly, several organisations within Australia are exploring the use of patient-derived organoids to predict response to treatment for colorectal, pancreatic and breast cancer patients.[51]

Regulatory approval and compliance

The formal consideration of non-animal model data in submission packages for clinical trial authorisation and regulatory compliance activities depends on that non-animal model's validation and acceptance for a specific application.

The FDA, the European Medicines Agency (EMA), and organisations like the Organisation for Economic Co-operation and Development (OECD) Test Guidelines Programme and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), have already validated and adopted protocols on a range of non-animal models. The internationally harmonised OECD Test Guidelines now include 22 protocols for non-animal models and corresponding applications.[52]

Leading international regulators are also adapting to the growing application of non-animal models through dedicated institutional programs, updated guidelines, analyses on the use of non-animal models, and in-house model testing.[53] For example, the FDA has established the Alternative Methods Group and the Innovative Science and Technology Approaches for New Drugs (ISTAND) pilot program, while the EMA has established the Innovation Task Force (ITF).[54] The FDA has already evaluated a range of medical product regulatory submissions including data from non-animal models: 115 involving 3D skin models, 760 involving spheroids, 83 involving organoids and 178 involving induced pluripotent stem cells.[55]

49 Li L, Knutsdottir H, Hui K, Weiss MJ, He J, Philosophe B, Cameron AM, Wolfgang CL, Pawlik TM, Ghiaur G, Ewald AJ, Mezey E, Bader JS, Selaru FM (2019) Human primary liver cancer organoids reveal intratumor and interpatient drug response heterogeneity. JCI Insight 4(2), e121490.

50 Associated Press (2017) Lab-made 'mini organs' helping doctors treat cystic fibrosis. In the lab. <https://www.statnews.com/2017/08/23/cystic-fibrosis-mini-organs-lab/> (accessed 11 July 2023).

51 Monash University (2018) Translating colorectal cancer organoids into patient care. Monash Biomedicine Discovery Institute. <https://www.monash.edu/discovery-institute/news-and-events/news/2018-articles/translating-colorectal-cancer-organoids-into-patient-care> (accessed 11 July 2023).

52 Pistollato F, Madia F, Corvi R, Munn S, Grignard E, Paini A, Worth A, Bal-Price A, Prieto P, Casati S, Berggren E, Bopp SK, Zuang V (2021) Current EU regulatory requirements for the assessment of chemicals and cosmetic products: challenges and opportunities for introducing new approach methodologies. Archives of Toxicology 95(6), 1867–1897.

53 US Food and Drug Administration (2022a) Advancing New Alternative Methodologies at FDA. FDA, Maryland, United States. <https://www.fda.gov/media/144891/download> (accessed 10 July 2023).

54 European Medicines Agency (2021) Innovation in medicines, Human regulatory - Research and development. <https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines> (accessed 10 July 2023); US Food and Drug Administration (2022b) Advancing Alternative Methods at FDA. <https://www.fda.gov/science-research/about-science-research-fda/advancing-alternative-methods-fda> (accessed 10 July 2023).

55 Avila A (2021) Microphysiological Systems (MPS): Bridging Human and Animal Research - An FDA/CDER Perspective. <https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.fda.gov%2Fmedia%2F147617%2Fdownload&wdOrigin=BROWSELINK> (accessed 10 July 2023).

2.3 Non-animal models over the next 15 years

2.3.1 Medical product development

Over the next 15 years, medical product development will see a reduction in animal model use globally. This reduction is likely to be accompanied by an increase in the use of non-animal models across all stages of the medical product development process. The most significant growth will likely come from complex in vitro models such as organoids and organ-on-chip technologies. In silico models are also expected to be more widely applied throughout the development process; used in conjunction with in vitro models to complement and validate findings. Figure 5 summarises the anticipated shifts in non-animal model use across the stages of the medical product development process.

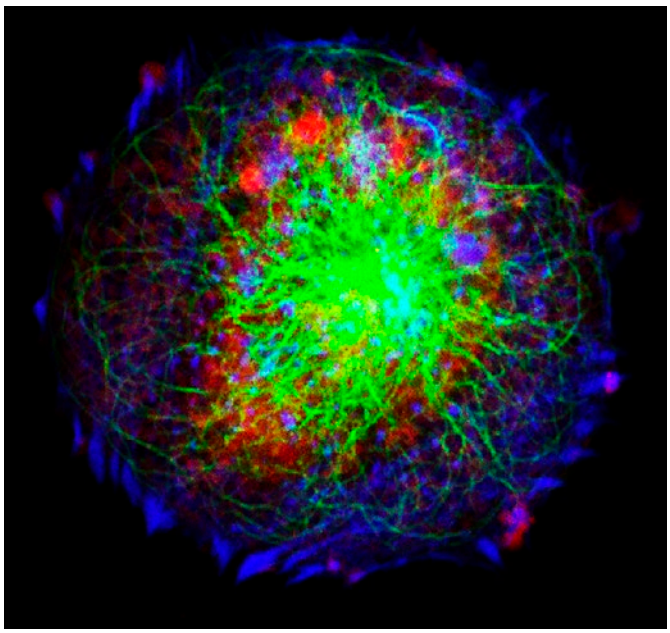


Figure 5. Expected shifts in the use of models for medical product development

	FUNDAMENTAL RESEARCH	DISCOVERY DEVELOPMENT	PRECLINICAL DEVELOPMENT	CLINICAL DEVELOPMENT	REGULATORY APPROVAL AND COMPLIANCE
Animal	↓	↓	↓		↓
In silico	↑	↑	↑	↑	↑
2D	↓	↓	↓		
3D	↑	↑	↑	↑	↑
OoC	↑	↑	↑	↑	↑
Tissue explant	↑	↑		↑	

Note: Model definitions can be found in Section 1.1

new application ↑ increasing application ↓ decreasing application

Fundamental research

Organoids and organ-on-chip technologies will likely complement and partially replace animal models in the exploration of physiological processes in fundamental research, particularly for monogenic disease modelling. However, implementing these models in fundamental research will require overcoming the financial challenges of running advanced cell culture techniques (i.e., acquiring highly specialised equipment and expensive consumables).

A transition to using human cells (either primary or derived from iPSCs) and more relevant biomaterials is highly probable for accurately modelling human diseases in fundamental research. More physiologically representative inputs can help uncover novel molecular hallmarks of disease (i.e., biomarkers), enhance the exploration of disease or condition mechanisms, and improve the predictivity of model responses to external compounds.

Bridging the gap between the outputs of in vitro models and clinical endpoints observed in an individual will likely remain an intense focus. This area will benefit from the continuous refinement of in silico approaches like quantitative systems pharmacology (QSP) and in vitro to in vivo extrapolation (IVIVE), which integrate large datasets of experimental data from in vitro models with mechanism-oriented mathematical (in silico) models. Emerging QSP and IVIVE models could then support the prediction of pharmacokinetic and pharmacodynamic endpoints, the evaluation of mechanisms of action, and dose estimations based on in vitro data.[56]

A greater exploration of digital twin approaches (an advanced in silico model), paired with personalised in vitro models, is also likely to emerge as an area of interest for fundamental research before finding more specialised uses in discovery and clinical development. These approaches seek to anticipate an individual's health outcomes based on key physiological parameters, medical data, and experimental responses.[57] Advancing the use of digital twins in healthcare is the target of recent projects like EDITH, which focuses on a multiscale virtual human twin, and In Silico World, which aims to support in silico models from validation to adoption.[58]

Discovery development

Target identification and validation will benefit from in silico models that integrate robust 'omics' data with outputs from complex in vitro models better representing human tissues (organoids, organ-on-chip, and tissue explants). Iteration between in vitro and in silico models may produce more comprehensive representations of human molecular pathways and networks in healthy and diseased states.

Compound screening and lead optimisation will likely continue transitioning to more complex in vitro 3D models like organoids. However, this is contingent on achieving technical improvements to reproducibility, well-characterised sizes and shapes, precise cellular populations, standardised output read-outs, and further cost reductions per data point. While organs-on-chips would be desirable for this activity, there is a need for significant increases in the throughput of this model type over the next 15 years.

Given the reliance on high-throughput platforms, discovery development activities will benefit the most from advances in automation, robotics, data analytics, and increasingly integrated in silico models. Such technologies can leverage complex models' increasing content and information density while helping offset their comparatively lower throughputs.

56 Azer K, Kaddi CD, Barrett JS, Bai JPF, McQuade ST, Merrill NJ, Piccoli B, Neves-Zaph S, Marchetti L, Lombardo R, Parolo S, Immanuel SRC, Baliga NS (2021) History and Future Perspectives on the Discipline of Quantitative Systems Pharmacology Modeling and Its Applications. Frontiers in Physiology 12, 637999; Bell SM, Chang X, Wambaugh JF, Allen DG, Bartels M, Brouwer KLR, Casey WM, Choksi N, Ferguson SS, Fraczkiewicz G, Jarabek AM, Ke A, Lumen A, Lynn SG, Paini A, Price PS, Ring C, Simon TW, Sipes NS, Sprankle CS, Strickland J, Troutman J, Wetmore BA, Kleinstreuer NC (2018) In vitro to in vivo extrapolation for high throughput prioritization and decision making. Toxicology in Vitro 47, 213–227.

57 EDITH Consortium (2022) European Virtual Human Twin. <https://www.edith-csa.eu/edith/> (accessed 11 July 2023); In Silico World (2023) The In Silico World Project. <https://insilico.world/project/> (accessed 11 July 2023); Venkatesh KP, Raza MM, Kvedar JC (2022) Health digital twins as tools for precision medicine: Considerations for computation, implementation, and regulation. npj Digital Medicine 5(1), 150.

58 In Silico World (2023) The In Silico World Project. <https://insilico.world/project/> (accessed 11 July 2023).

Preclinical development

For both toxicology and pharmacology, animal models are likely to be partially displaced by the increased adoption of complex in vitro models that better mimic human tissue structures, dynamics, and behaviours (i.e., organoids and organ-on-chip). Developing multi-organ models and simulating increasingly complex tissue interactions will be technical priorities to enable truly systemic toxicology and pharmacokinetic assessments in vitro. Modelling these interactions will be facilitated by organ-on-chip models where different tissues are cultured in independent modules and connected to each other. QSP or IVIVE in silico models can complement this approach to translate findings to a human scale.

The use of non-animal models in conducting preliminary toxicity screens and informing prioritisation strategies will enable a reduction in the number of animals used during late-phase preclinical development. Animal use reductions can stem from the earlier discontinuation of candidates with clear hazard signals in vitro or from the accumulation of robust toxicology and pharmacology data that allows animal testing to serve as a limited confirmatory or regulatory step where still required. Non-animal models for organ-specific toxicology will rely on developing, characterising and validating these models for specific contexts of use. These are clearly defined test-output combinations where model use is considered valid, with resulting data accepted by regulators for decision-making.

Clinical development

Future non-animal model use in support of clinical development could occur at four levels: informing the decision to advance a medical product to clinical trials, planning study populations and informing participant stratification in clinical trials, investigating adverse events during clinical trials, and developing personalised therapeutic regimens.

Even after approval from a regulator based on preclinical data, the formal decision to advance a candidate into clinical trials carries uncertainty and financial risk. Trial pre-screening using models derived from prospective participants (organoids, organs-on-chips, and tissue explants) could allow candidates to 'fail early' in clinical development and avoid the significant time and resources involved in clinical studies.

If the decision to proceed to clinical trials is made, personalised models could also be used to develop targeted inclusion, exclusion and stratification criteria for clinical trial participants.[59] Preliminary testing of candidates in models from prospective participants may help identify population differences that impact safety or efficacy, explore their underlying mechanisms, and build study designs that better consider variations due to gender, age, genetic background or co-occurring diseases. Establishing and storing in vitro models from trial participants could facilitate the investigation of adverse events during (or after) clinical trials and explore adverse outcome pathways for a failed candidate.

In the clinical setting, scalable non-animal models for personalised drug screening may be enabled by further advancements in iPSC derivation, tissue explant culture, integration of genomics and the overall cost of personalised approaches. There could be a reduction in the time required for iPSC derivation from adult tissue to match clinical timelines better and implementation of in-depth characterisation of both the starting biological material and the cells produced. Similarly, tissue explant culture strategies will require improvement to preserve native properties over longer periods, while increasing interactions with genomics may help link patient-specific genetic variants with drug responses observed in vitro. Finally, overall reductions in cost will be necessary to make this application of non-animal models possible at scale.

59 National Center for Advancing Translational Sciences (2020) Clinical Trials on a Chip, Tissue Chip Initiatives & Projects. <https://ncats.nih.gov/tissuechip/projects/clinical-trials> (accessed 11 July 2023).

Regulatory approval and compliance

Incorporating non-animal models into routine use for regulatory approvals will be incremental. Novel non-animal models will have to be validated by independent centres, qualified by large regulators, and accepted for specific contexts of use by international harmonisation organisations. However, this is a sequential process, and in the short term, regulators are likely to prioritise the standardisation of the qualification process itself over international harmonisation. This prioritisation is due to the length of such a process, the impact of the international guidance produced, and the rapid development of increasingly complex models. An initial focus on the qualification process can allow the continual definition of specific contexts of use for new models, prevent a premature outdating of international guidelines for non-animal model use and provide sufficient flexibility for the evolving field.

In silico, in vitro 3D, and organ-on-chip models will see faster adoption in simple hazard categorisation for product labelling and assessing products posing a lower or well-established level of concern for regulators (like non-prescription medications or certain regulated pharmaceutical ingredients). These regulatory applications are the most suitable in the short term given their simple assay outputs, the pre-existence of safety data for known substances, and the data quality that non-animal models can produce.

In regulatory compliance applications, in silico, in vitro 3D, and organ-on-chip models could also be used for lower-concern products or well-known pharmaceutical ingredients that require testing before batch release. These models would reduce repetitive and animal-intensive tests. For example, US agencies have identified a potency assay for botulinum toxin as a priority area for non-animal model adoption.[60] Similarly, vaccine batch testing via non-animal alternatives (including in silico and in vitro models) has been the focus of the VAC2VAC project in the EU.[61]

2.3.2 Organ models

Across complex applications, like disease modelling in fundamental research or organ toxicity testing in preclinical development, the landscape of non-animal model readiness for wider adoption varies by organ system. Table 3 summarises several key organ systems, including currently used non-animal model types, example non-animal model applications, and an assessment of the likelihood that these models will displace the status quo within the next 15 years. The organ systems for which non-animal models are the most likely to disrupt the status quo are the cardiovascular, respiratory, digestive (gastrointestinal), and integumentary systems, along with the eye and liver as specific organs.

The future state categorisation is based on currently leading non-animal model types, their existing technical limitations (see Appendix A.2), and the organ-specific challenges to achieving greater physiological similarity. Table 3 was informed through literature review and stakeholder reviews. Specific modelling applications in each organ system vary significantly by model type, disease, and medical product of interest. Therefore, the readiness of a specific organ-model-application combination over the next 15 years could be more advanced than the organ system's overall state presented here.

60 US Department of Health and Human Services (2023) RFA-TR-22-031: Botulinum Toxin Potency Assay using Tissue Chips (BoT PATCh) (UT1, UT2 Clinical Trail Not Allowed). Grants. <https://grants.nih.gov/grants/guide/rfa-files/RFA-TR-22-031.html> (accessed 11 July 2023).

61 European Vaccine Initiative (2023) Vaccine batch to vaccine batch comparison by consistency testing. VAC2VAC EU. <https://europevaccine.wixsite.com/vac2vac-eu> (accessed 11 July 2023).

Table 3. Potential of emerging organ models to displace the status quo within the next 15 years.

ORGAN SYSTEM	CURRENT ADVANCED MODEL TYPES	EXAMPLE APPLICATION	FUTURE STATE
Cardiovascular system – heart	In silico 3D (Organoid) Organ-on-chip	Drug-induced arrhythmia testing	
Respiratory system – lungs	Tissue explant Organ-on-chip	Pulmonary fibrosis model	
Digestive (gastrointestinal) system	In silico 3D (Organoid) Organ-on-chip	Drug absorption and transport modelling	
Integumentary system – skin	3D (Scaffold) Tissue explant	Wound healing and skin regeneration modelling	
Eye	3D (Scaffold) 3D (Organoid) Organ-on-chip	Retinogenesis and genetic retinal disease modelling (e.g., Stargardt's macular degeneration)	
Metabolic and endocrine – liver	In silico Organ-on-chip	Non-alcoholic fatty liver disease model	
Nervous system – central and peripheral	In silico 3D (Organoid) Organ-on-chip	Neuromuscular junction model for ALS mechanism modelling and therapeutic response testing	
Metabolic and endocrine – pancreas	3D (Organoid) Organ-on-chip	Pancreatic cancer and cystic fibrosis drug screening	
Renal and urogenital – kidney	3D (Organoid)	Kidney polycystic disease modelling or drug-induced nephrotoxicity testing	
Musculoskeletal system	3D (Organoid) Organ-on-chip	Myogenesis and muscle regeneration model	
Reproductive system	3D (Organoid) Tissue explant	Reproductive toxicity and endometriosis modelling	
Ear	3D (Organoid)	Genetic disease-associated hearing loss modelling and corrective gene therapy testing	
Hemic (blood) system – bone marrow	3D (Organoid) Organ-on-chip	Bone marrow niche and haematopoiesis modelling	
Inflammatory disorders and the immune system	3D (Organoid) Organ-on-chip	Immune activation and response in a lymph node model for influenza vaccine testing	

FUTURE STATE	
	Non-animal models demonstrate equivalent, or better, outputs than animal models and are likely to replace animal models for this organ system in the next 15 years.
	Non-animal models demonstrate the potential to replicate animal model outputs; further advances could position them to replace or complement animal models for this organ system in the next 15 years.
	Non-animal models still need to demonstrate equivalent outputs to existing animal models, will require further advances to complement animal models, and are unlikely to replace animal models for this organ system in the next 15 years.

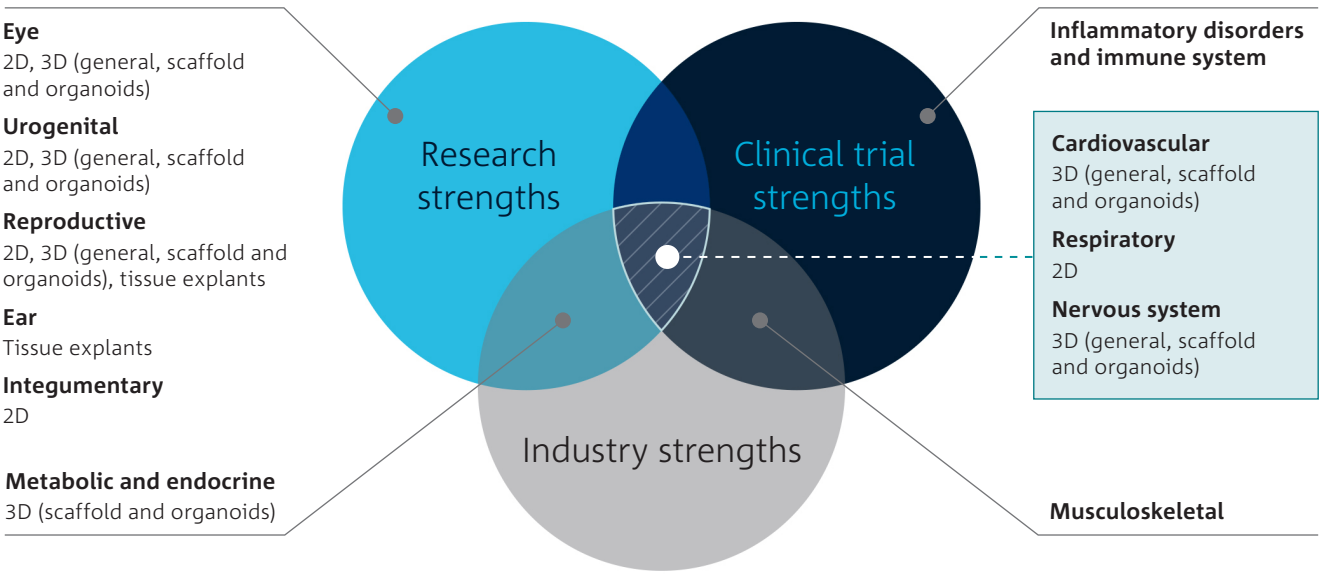
3 Non-animal models in Australia

Australia's medical product development ecosystem is active across all organ systems, with each stakeholder group (research, clinical trials, and industry) demonstrating specific strengths (Figure 6).

CSIRO Futures identified strengths across all stakeholder groups for the cardiovascular, respiratory and nervous systems. Research strengths not yet translated into clinical trials or industry strengths are areas to expand Australian commercial offerings.

Comparative national strengths were assessed via publication counts for organ system-model type combinations, clinical trial registrations by condition, and company counts by therapeutic area. Research strength was determined by output to enable a consistent examination across areas (where impact metrics may be an inadequate measure due to a small number of publications) and to support comparison to other countries. Organ system-model type combinations not identified as comparative strengths in this analysis should not be interpreted as an absence of high-quality research or a lack of mature models with potential for commercial translation. Appendix A.3 outlines further information regarding the methodology and results.

Figure 6. Alignment of strengths in Australia's medical product development ecosystem



3.1 Research strengths

Australia is internationally regarded for its research capability in non-animal models for several specific organ systems. Between 2018 and 2023, Australia's share of non-animal model publications was above 3% and ranked in the top 10 globally for specific organ system-model type combinations, as shown in Table 4.

Cancer, as a therapeutic area, is not represented in the organ system-model type assessment of research strengths, given its broad inclusion of multiple organ systems simultaneously. However, cancer research was noted by consulted stakeholders as an area of strength for Australia and 'childhood cancer' emerged as a topic of comparative strength in a separate bibliometric analysis, ranking 5th in the world by publication output.[62]

Stakeholders also noted that Australian researchers possess world-leading expertise in toxicology, immunology, infectious diseases, blood/haematopoietic system research, and genetic and rare disease characterisation. While these specialties are not presented in terms of non-animal model publications and ranking, they represent additional areas of capability that could be leveraged to support non-animal model offerings domestically and abroad.

Existing research strength in non-animal models can unlock economic benefits for Australia, given industry interest, expanding applications, and growing markets. The global organoid market in 2022 was $1.62 billion and is expected to reach $30.91 billion by 2040, with a CAGR of 17.4%. This market is estimated to generate **$1.28 billion** in revenue and 4,200 jobs for Australia by 2040.[63] For comparison, the organ-on-chip market is at an earlier phase of adoption. It was valued at $110 million worldwide in 2022, with a projection of $11.48 billion by 2040 (29.4% CAGR). The potential share for Australia by 2040 is **$310 million** in revenue, with 700 related jobs.[64]

Table 4. Organ system-model type combinations emerging as comparative research strengths for Australia, based on the share of global publication output and corresponding global position between 2018 and 2023.

ORGAN SYSTEM	MODEL TYPE	AU PERCENTAGE OF GLOBAL	GLOBAL POSITION
Eye	3D (Scaffold and organoid)	7.5%	5th
	3D (General)	6.0%	6th
	2D	4.7%	6th
Urogenital system	2D	4.0%	6th
	3D (General)	4.7%	7th
	3D (Scaffold and organoid)	6.2%	8th
Reproductive system	3D (Scaffold and organoid)	6.1%	7th
	2D	4.6%	7th
	3D (General)	4.7%	8th
	Tissue explant	4.6%	10th
Cardiovascular system	3D (Scaffold and organoid)	4.5%	7th
	3D (General)	3.7%	10th
Ear	Tissue explant	5.0%	8th
Respiratory system	2D	4.2%	10th
Nervous system	3D (Scaffold and organoid)	4.0%	10th
	3D (General)	3.4%	12th
Integumentary system	2D	3.6%	10th
Metabolic and endocrine systems	3D (Scaffold and organoid)	3.4%	11th

62 An InCites analysis of the Childhood Cancer Area (Citation Topics – Micro) shows Australia ranks 5th in the world by number of Web of Science articles in the last 5 complete years (262 in 2018 – 2022), and 9th among the subset of top 15 countries when considering Category Normalized Citation Impact (1.36); US National Cancer Institute (2023) Childhood Cancer Model Atlas. Childhood Cancer Data Initiative - Data Catalog. <https://datacatalog.ccdi.cancer.gov/dataset/VPCC-CCMA> (accessed 11 July 2023).

63 Based on CSIRO Futures economic analysis of global non-animal model market size data, Australian share of global publications by model, and national wage data. See Appendix A.5 for the methodology used.

64 Based on CSIRO Futures economic analysis of global non-animal model market size data, Australian share of global publications by model, and national wage data. See Appendix A.5 for the methodology used.

3.2 Clinical strengths

Australia has world-leading clinical trials infrastructure, with over 50 trial networks offering Phase I–III trials. Australia also provides a range of grants, tax incentives and Patent Box schemes, which makes the country an attractive destination for conducting clinical trials.[65] Between 2018 and 2023, close to 10,000 clinical trials were registered in Australia, with nervous, cardiovascular, respiratory, musculoskeletal, and immune systems having the highest number throughout the period.[66]

Australia has registered clinical trials across all organ systems identified as areas of research strength. However, the distribution of trials per organ system does not yet reflect the strengths, highlighting potential gaps and unexploited opportunities. For example, Australia's globally recognised expertise in non-animal models developed locally for eye, urogenital and reproductive systems have not yet translated into increased clinical trial activity.

3.3 Industry strengths

Australia's industry capabilities related to non-animal model use in medical product development are highly research-led. The market is driven by ad-hoc research collaborations between research institutions and pharmaceutical companies, and start-ups that have typically spun out from research institutions. As such, this report takes a broader definition of the industry, to include organisations with non-animal model products or services that are sufficiently mature to be provided for a fee.

In total, 37 Australian organisations were identified to have mature non-animal model-related capabilities through stakeholder consultation and desktop analysis (Figure 7). Given the existence of ad-hoc research collaborations and the ongoing maturation of national industry capabilities, this is likely an underestimate of the entire commercial ecosystem.

Australia possesses industry capabilities across all non-animal model types. In vitro 2D is the most common model type used in service offerings, with 23 organisations (predominantly research institutions) providing this, typically through HTS platforms.

Australia also has market-supporting entities, including contract research organisations (CROs), which contribute to the commercialisation of non-animal models by providing related clinical trial and research support services. One such entity is Phenomics Australia, which provides infrastructure and supporting services through their partner network to enable in vitro genome engineering and disease modelling, 3D bioprinting, organoid production, human iPSCs derivation, patient-derived cell line sourcing, and high-throughput screening.[67]

Figure 7. Summary of the Australian non-animal model industry landscape

25	Research institutions
9	Companies
3	Contract research organisations

See Appendix A.4 for the full organisation list.

65 Australian Trade and Investment Commission (2022) Insight – Australia: A go-to destination for clinical trials. <https://www.austrade.gov.au/news/insights/insight-australia-a-go-to-destination-for-clinical-trials> (accessed 11 July 2023).

66 Based on an ANZCTR search of registered clinical trials between 2018 and 2023. See Appendix A.3 for the methodology used and results for the top 5 organ systems.

67 Phenomics Australia (2023a) In vitro Genome Engineering & Disease Modelling. <https://phenomicsaustralia.org.au/in-vitro-genome-engineering-disease-modelling/> (accessed 11 July 2023).

3.4 Funding and investment

Funding of non-animal models within Australia is mainly indirect, with no large public or private investment schemes specifically dedicated to their development, validation, or commercialisation. Stakeholders noted that the funding enabling non-animal model development primarily comes from National Health and Medical Research Council (NHMRC) schemes[68] and Medical Research Future Fund (MRFF) initiatives.[69] For example, non-animal model activity benefits from the MRFF Australian Stem Cell Therapies Mission funding of $150 million over ten years.[70]

Funding for NCRIS also supports non-animal model development, through access to genome engineering, sequencing, functional genomics, histopathology, stem cell derivation and disease modelling capabilities; activities supported by Phenomics Australia across its network.[71] Stakeholders noted that NCRIS support and funding from Phenomics Australia have been instrumental in developing organ modelling strengths by individual research groups and institutions.

Given the lack of dedicated funding programs, researchers also turn to pharmaceutical company partnerships, privately funded fellowships, and philanthropic organisations to support the expansion of local capabilities and broader model development projects. An example of this is the historical backing from the Medical Advances Without Animals Trust (MAWA), which provides direct contributions and helps steer external funding into relevant non-animal model research.

Funding for the commercial translation of non-animal models, especially from venture capital, is also limited in Australia. As a result, while innovative non-animal models are developed with local talent, the vehicles to commercialise them are often established internationally, forcing novel developments offshore (e.g., Dynomics in the US and Mogrify in the UK).[72]

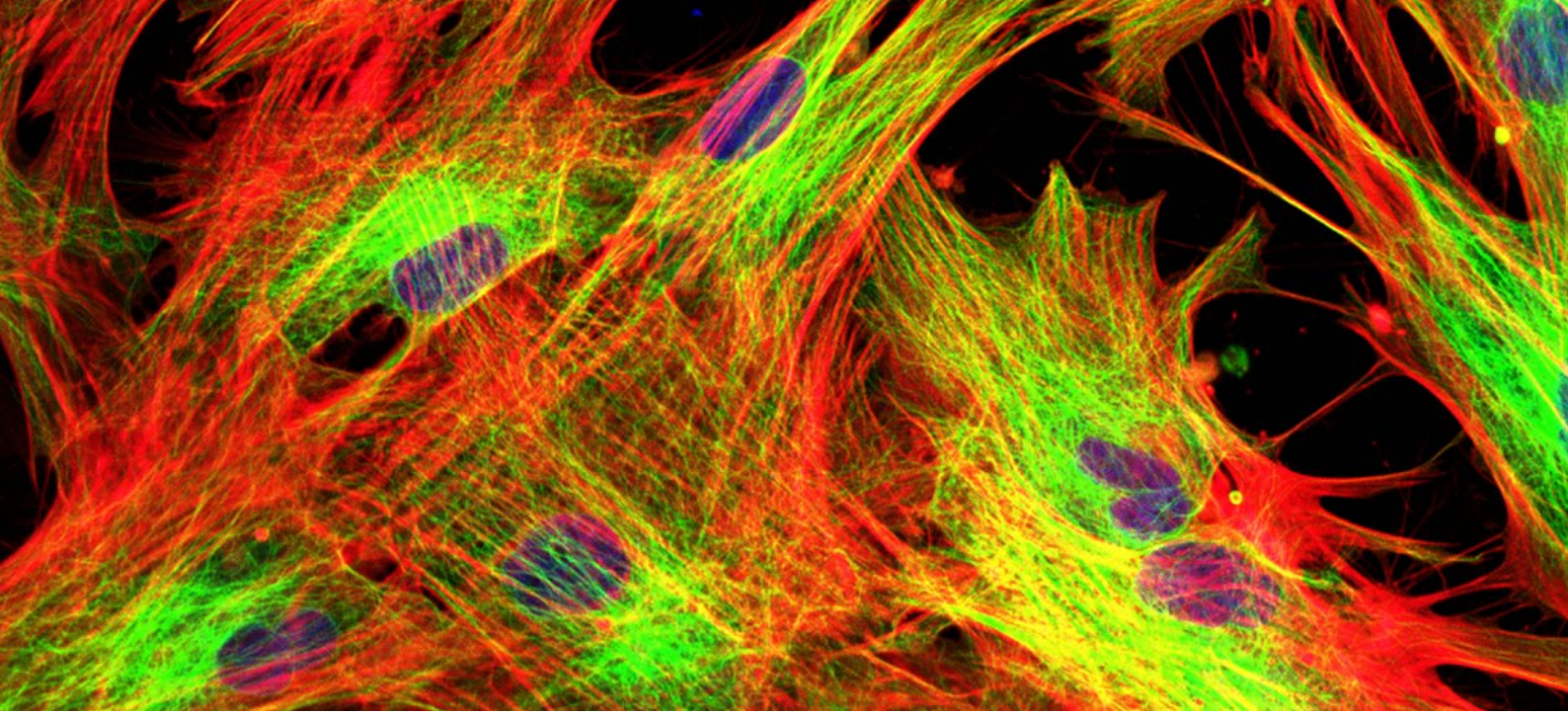
68 National Health and Medical Research Council (2022) Research funding statistics and data. Funding - Data on Research. <https://www.nhmrc.gov.au/funding/data-research/research-funding-statistics-and-data> (accessed 11 July 2023).

69 Australian Government Department of Health and Aged Care (2022) All MRFF initiatives. Medical Research Future Fund <https://www.health.gov.au/our-work/medical-research-future-fund/all-mrff-initiatives> (accessed 11 July 2023).

70 Australian Government Department of Health and Aged Care (2023) Stem Cell Therapies Mission. Our work. <https://www.health.gov.au/our-work/stem-cell-therapies-mission> (accessed 11 July 2023).

71 Phenomics Australia (2023b) Our expertise. <https://phenomicsaustralia.org.au/expertise/> (accessed 11 July 2023).

72 Dynomics (2022) Dynomics - Therapies to Restore Heart Function. <https://www.dynomics.com/#technology> (accessed 11 July 2023); Mills RJ, Parker BL, Quaife-Ryan GA, Voges HK, Needham EJ, Bornot A, Ding M, Andersson H, Polla M, Elliott DA, Drowley L, Clausen M, Plowright AT, Barrett IP, Wang Q-D, James DE, Porrello ER, Hudson JE (2019) Drug Screening in Human PSC-Cardiac Organoids Identifies Pro-proliferative Compounds Acting via the Mevalonate Pathway. Cell Stem Cell 24(6), 895-907; Mogrify (2023) Mogrify - Reprogramming Health. <https://mogrify.co.uk/> (accessed 11 July 2023).



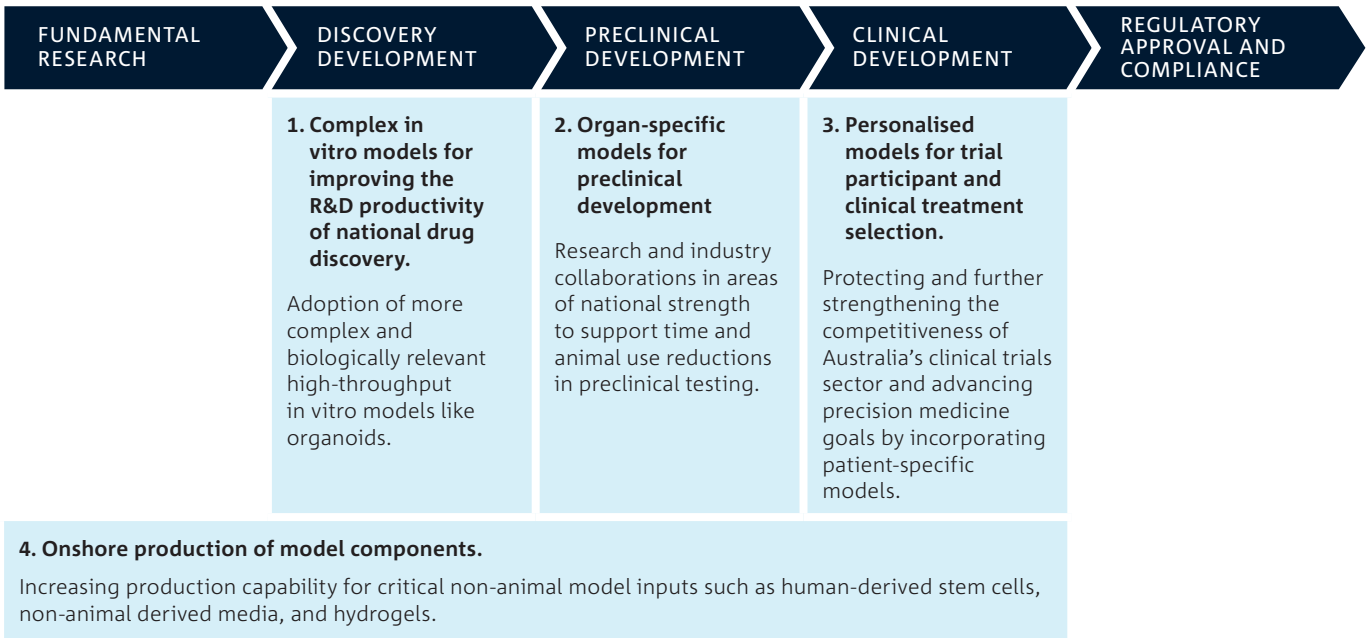
4 National opportunities and recommendations

4.1 National opportunities

With other nations already leading the way in some non-animal model applications and offerings, it is important for Australia to focus on leveraging research, clinical and industry strengths to pursue near- and medium-term opportunities.

This report defines opportunities as any non-animal model product or service offering that could benefit the quality of domestic R&D activities or create revenue streams. The analysis of national strengths and insights from 103 stakeholders around areas of greatest need identified four opportunities for Australia (Figure 8).

Figure 8. Four national opportunities



4.1.1 Complex in vitro models for improving the R&D productivity of national drug discovery

The opportunity

Discovery development relies extensively on HTS to source novel therapeutic targets, identify compounds exhibiting activity against them, and assess preliminary hits. HTS uses miniaturised models, concurrent screening, and streamlined visualisation or detection of outputs to support large-scale testing within reduced timeframes. The technical requirements of HTS have traditionally resulted in in vitro 2D models being used for most discovery activities, at the expense of greater complexity and biological relevance.

Improvements to the activity of Australian HTS platforms and drug discovery programs could be made by adopting more biologically relevant but still high-throughput complex in vitro models like organoids. While more complex in vitro models are unlikely to fully match the throughput offered by in vitro 2D models, wider adoption at the earliest stage of development could increase the likelihood of identifying relevant targets, reduce late-stage attrition of locally developed candidates, and increase the productivity of the domestic pipeline.[73] In instances where in vitro 2D is still selected as the primary model type for HTS, using organoids for secondary screens can narrow a potentially large number of initial hits.[74] This complementary use could reduce false positives and increase confidence in compounds selected for further development.

Why Australia?

Australia has an existing base of discovery platforms with HTS capabilities (See Appendix A.4). These platforms facilitate the transition from fundamental research into preclinical development by identifying hits, promoting intellectual property (IP) generation and, in some cases, de-risking discovery activities through government-subsidised screens.[75]

The emergence of Australian facilities capable of producing more complex, HTS-compatible in vitro models at a large scale, with high reproducibility and minimal cost, can help support national discovery platforms. Case study 1 presents one such facility, with the emergence of others necessary to strengthen the local R&D ecosystem.

Australia also possesses an overarching national discovery and development network supported by NCRIS. Organ system-specific strengths like those outlined in Section 3.1 could complement existing national discovery platforms by providing organ- and tissue-specific models for specialised HTS during early development.

CASE STUDY 1: Australian Organoid Facility – Large-scale production of organoids for HTS

The Australian Organoid Facility (AOF) has invested in state-of-the-art automation, high-content imaging, and analysis capabilities to produce high-quality, reproducible organoids that can be used for HTS. The AOF is located at the Australian Institute for Bioengineering and Nanotechnology (AIBN) at the University of Queensland.

The AOF provides domestic research and industry services across model development, high-throughput organoid production, and drug and functional screening. The facility specialises in brain, kidney, blood vessel and cancer organoids, with a vision of expanding to cardiac, intestinal, liver and respiratory models. The detailed requirements and specific protocols used for organoid production vary across tissue types, resulting in different cost ranges. However, as an example, the AOF currently provides brain organoids for $30 to $60 each, depending on culture time and mode of production.[76] A focus on automation, progressively optimised culture protocols, and scale will enable a reduction in production costs over time.

73 Ekert JE, Deakyne J, Pribul-Allen P, Terry R, Schofield C, Jeong CG, Storey J, Mohamet L, Francis J, Naidoo A, Amador A, Klein J-L, Rowan W (2020) Recommended Guidelines for Developing, Qualifying, and Implementing Complex In Vitro Models (CIVMs) for Drug Discovery. SLAS Discovery 25(10), 1174–1190.

74 Mills RJ, Parker BL, Quaife-Ryan GA, Voges HK, Needham EJ, Bornot A, Ding M, Andersson H, Polla M, Elliott DA, Drowley L, Clausen M, Plowright AT, Barrett IP, Wang Q-D, James DE, Porrello ER, Hudson JE (2019) Drug Screening in Human PSC-Cardiac Organoids Identifies Pro-proliferative Compounds Acting via the Mevalonate Pathway. Cell Stem Cell 24(6), 895-907.

75 The Walter and Eliza Hall Institute of Medical Research (2023) Advancing the latest discoveries - National Drug Discovery Centre (NDDC). The National Drug Discovery Centre <https://nddc.wehi.edu.au/> (accessed 11 July 2023).

76 Price range and accompanying rationale provided by the AOF.

4.1.2 Organ-specific models for preclinical development

The opportunity

Non-animal models that better replicate organ and disease physiology can enable more relevant and predictive testing. In turn, this can support animal model use rationalisation, reduced attrition rates during clinical development, and enhanced safety and efficacy profiling of therapeutic candidates. Non-animal models can also enable time and animal use reductions in preclinical testing. Table 5 illustrates this, comparing the cost, time, and animal use across two validated OECD toxicity tests; one using an animal model and the other using an equivalent non-animal approach. Additional comparisons and the methodology employed can be found in Appendix A.5.

The development, validation, and standardisation of improved organ and disease models in the Australian ecosystem could potentially support three distinct business models:

1. **Commodities:** Non-animal models as commercialised products for academic researchers and pharmaceutical R&D teams, as exemplified by the growing organ-on-chip market.[78]
2. **Services:** Non-animal models as validated assays for CRO service provision in niche areas, sought by pharmaceutical companies to cover highly specific in-house development gaps.
3. **Partnerships:** Non-animal models as versatile platforms for developing and testing many different medical product candidates. Effectively, means of continuous IP generation and enablers of partnerships between model developers and pharmaceutical companies for larger discovery and preclinical development projects.

Table 5. Comparison between OECD test guidelines (TG) featuring equivalent animal and non-animal approaches for acute dermal corrosion across cost, time, and animal use.[77]

TYPE OF TOXICITY	OECD TG	TEST TYPE	STUDY COST (AUD 2022)	TIME DURATION (DAYS)	NUMBER OF ANIMALS USED
Acute dermal irritation/ corrosion	404	Animal	2,000	15.00	2
Membrane barrier test method for skin corrosion	435	In vitro	4,100	0.2	0
Difference			**2,100**	**–14.8**	**–2.00**

77 Adapted from: Marty MS, Andrus AK, Groff KA (2022) Animal metrics: Tracking contributions of new approach methods to reduced animal use. ALTEX – Alternatives to animal experimentation 39(1), 95–112; Meigs L., Smirnova L, Rovida C, Leist M, Hartung T (2018) Animal testing and its alternatives – the most important omics is economics. ALTEX – Alternatives to animal experimentation 35(3), 275–305; CSIRO Futures calculations.

78 Zhang B, Radisic M (2017) Organ-on-a-chip devices advance to market. Lab on a Chip 17(14), 2395–2420.

Why Australia?

Australia has several characteristics that are key to enabling the production of organ- and patient-specific models. These include a diverse population, close collaboration between clinical and research settings, internationally recognised and geographically distributed capacity for iPSC generation (important for complex in vitro model development),[79] and a focus on genomics capabilities. As described in Section 3.1, Australia has globally competitive modelling and research strengths in various areas. These areas could inform initial investment priorities that enhance national-scale capabilities in organ-specific toxicology and pharmacology testing.

The research-intensive focus of the Australian landscape makes the partnership business model a strategic option in the short to medium term. Partnerships provide pharmaceutical companies with access to both the research expertise behind a promising non-animal model and to the local capabilities of an institution or biomedical precinct. In turn, the institution or precinct benefits from direct investment, industry-relevant training, knowledge transfer, increased activity for supportive research services and IP production that can be out-licensed to attract royalties over time. Case Study 2, the reNEW consortium, exemplifies the viability and relevance of the partnership model.

CASE STUDY 2: Pluripotent stem cell and in vitro modelling expertise as drivers of international partnerships

reNEW is a tripartite collaboration between the University of Copenhagen in Denmark (governing hub), the Leiden University Medical Center in the Netherlands, and the Murdoch Children's Research Institute (MCRI) in Australia. reNEW conducts stem cell research in three areas: regenerative medicine strategies for damaged tissues, drug screening in human models, and genetic disease therapies enabled by gene editing. Underpinning the collaboration is a EUR 300 million grant from the Novo Nordisk Foundation distributed over ten years between the partnering institutions.[80]

The MCRI was selected as a node due to its internationally recognised expertise in pluripotent stem cells and connections across the Melbourne Biomedical Precinct.[81] The MCRI node possesses stem cell biology expertise in urogenital (kidney, specifically), cardiovascular, blood, musculoskeletal, respiratory, and nervous system applications.[82] The node's expertise in iPSCs underpins strong organ and disease modelling capabilities across the noted organ systems. This is illustrated by organ-specific modelling projects, such as evaluating infectious agents in a stem cell-derived lung model, understanding paediatric leukaemia development in bone marrow models, or testing novel drugs for neurodevelopmental conditions in brain models.[83]

79 An InCites analysis of the Stem Cell Research Area (Citation Topics – Meso) ranks Australia 15th in the world by number of Web of Science articles in the last 5 complete years (764 in 2018 – 2022), and 6th among the subset of top 15 countries when considering Category Normalized Citation Impact (1.37). Moreover, iPSCs was consistently noted by consulted stakeholders as an area of recognition and comparative strength.

80 Novo Nordisk Foundation (2022) Novo Nordisk Foundation Center for Stem Cell Medicine (reNEW). Projects. <https://novonordiskfonden.dk/en/projects/novo-nordisk-foundation-center-for-stem-cell-medicine-renew/> (accessed 11 July 2023).

81 Murdoch Children's Research Institute (2022a) reNEW - Novo Nordisk Foundation Center for Stem Cell Medicine. About. <https://www.mcri-renew.org.au/about/> (accessed 11 July 2023).

82 Murdoch Children's Research Institute (n.d.) Stem Cell Biology. Research areas. <https://www.mcri.edu.au/research/research-areas/stem-cell-biology> (accessed 11 July 2023).

83 Murdoch Children's Research Institute (2022b) Using stem-cell models of the lung to identify cellular therapies for Rhinovirus - reNEW - Novo Nordisk Foundation Center for Stem Cell Medicine. Our research. <https://www.mcri-renew.org.au/our-research/using-stem-cell-models-of-the-lung-to-identify-cellular-therapies-for-rhinovirus/> (accessed 11 July 2023); Murdoch Children's Research Institute (2022c) Modelling childhood leukaemia to better understand the disease – reNEW – Novo Nordisk Foundation Center for Stem Cell Medicine. Our research. <https://www.mcri-renew.org.au/our-research/generating-models-of-childhood-leukaemia-to-better-understand-the-disease/> (accessed 11 July 2023); Murdoch Children's Research Institute (2022d) Developing a drug screening platform for neurological diseases - reNEW - Novo Nordisk Foundation Center for Stem Cell Medicine. Our research. <https://www.mcri-renew.org.au/our-research/developing-a-drug-screening-platform-for-neurological-diseases/> (accessed 11 July 2023).

4.1.3 Personalised models for trial participant and clinical treatment selection

The opportunity

Personalised non-animal models such as organoids and organs-on-chips possess the potential to inform clinical trials, improve the safety of participants, and support the assessment of the clinical efficacy of medical product candidates.

Personalised models can assist in the screening, selection, and stratification of shortlisted participants for clinical trials by providing an initial assessment of their unique response to a therapeutic candidate. This information can increase participant safety and reduce development costs by identifying adverse effects earlier. This application is best suited for medical product development for rare diseases (due to limited population sizes); emerging infectious diseases (due to the ethical constraints on conducting human trials, especially for infectious diseases with high mortality rates); cancers (given the ability to collect sufficient tissue samples from patients to generate organoids and conduct tests that effectively inform treatment decisions); and eye diseases (with Australia's expertise in eye research, the anatomical limitations of conducting trials in patient eyes, and the prevalence of eye disease).

Personalised non-animal models can also be used in precision medicine, benefitting patients by screening safety and efficacy responses to shortlisted therapeutics without impacting the patient directly. This use supports treatment selection and may be primarily suitable for testing cancer treatments, due to patients' sensitivity to treatment and the availability of tissue samples.[84] Assessing treatments of diseases with a strong genetic basis (where treatment options are highly susceptible to genetic variability), such as cystic fibrosis and rare diseases, is also a viable focus.

Personalised models also create the opportunity for label indication expansion (the identification of new uses for already approved therapeutics).

While few trials have used non-animal models to inform therapy selection to date, approximately 180 planned, active, or completed clinical trials globally have utilised organoid models as part of their study.[85]

Why Australia?

Australia has an established clinical trials sector, contributing $1.4 billion to the Australian economy in 2019.[86] With personalised non-animal models in clinical trials likely to grow over the coming years, ensuring Australia develops this capability will be necessary for maintaining and further advancing the sector's competitiveness.

The clinical application of these models is a form of precision medicine, a priority science capability for Australia.[87] Development of non-animal models for clinical applications currently receives funding via MRFF initiatives related to precision medicine, including the Clinicians Researchers Initiative and Genomic Health Futures Mission, which will invest $200 million and $500 million, respectively.[88] Many of the skills and infrastructure required for precision medicine are also transferrable to this opportunity's trial participant selection applications.

While yet to be implemented at scale, research groups across Australia are actively investigating the use of patient-derived organoids to predict colorectal, pancreatic and breast cancer responses to treatment, as highlighted in Case Study 3.

84 Chen X, Sifakis EG, Robertson S, Neo SY, Jun S-H, Tong L, Hui Min AT, Lövrot J, Hellgren R, Margolin S, Bergh J, Foukakis T, Lagergren J, Lundqvist A, Ma R, Hartman J (2023) Breast cancer patient-derived whole-tumor cell culture model for efficient drug profiling and treatment response prediction. Proceedings of the National Academy of Sciences 120(1), e2209856120.

85 Based on a search of ClinicalTrials.gov using 'organoids' as the only keyword in the Other terms field, without time or location restrictions. Excludes suspended, terminated or withdrawn studies. <https://clinicaltrials.gov/ct2/results?term=organoids&map=CA > (accessed on 07 July 2023).

86 MTPConnect (2021) Australia's Clinical Trials Sector: Advancing innovative healthcare and powering economic growth. <https://www.mtpconnect.org.au/images/MTPConnect_Australia's%20Clinical%20Trials%20Sector%20report%202021.pdf> (accessed 10 July 2023).

87 Australian Government Department of Education (2021) 2021 National Research Infrastructure Roadmap. <https://www.education.gov.au/national-research-infrastructure/resources/2021-national-research-infrastructure-roadmap> (accessed 11 July 2023).

88 Australian Government Department of Health and Aged Care (2022) All MRFF initiatives. Medical Research Future Fund <https://www.health.gov.au/our-work/medical-research-future-fund/all-mrff-initiatives> (accessed 11 July 2023).

CASE STUDY 3: Translating colorectal cancer organoids into patient care

The Monash Biomedicine Discovery Institute, in partnership with Cabrini Health, the University of Melbourne, the Peter MacCallum Cancer Centre, the South Australian Health and Medical Research Institute (SAHMRI) and The Walter and Eliza Hall Institute of Medical Research (WEHI), has developed a colorectal cancer organoid platform for patient care and has demonstrated the potential use of organoids for treatment selection.

The initiative, funded by Cancer Australia's Priority-driven Collaborative Cancer Research Scheme (PdCCRS), has found that patient-derived colorectal cancer organoids retain key characteristics of the tissue from which they are derived. The colorectal organoid platform is derived from 50 patient tumours, normal adjacent tissue and, in some cases, matched metastatic tumours from the same patients. While work is underway to ensure this translates into the clinic, this research is a strong step towards utilising organoids to assess individual patients' drug sensitivities and guide therapy selection.[89]

89 Cabrini Health (2022) New research puts personalised treatment for colorectal cancer on the cards. Research. <https://www.cabrini.com.au/organoids/> (accessed 11 July 2023); Monash University (2018) Translating colorectal cancer organoids into patient care. Monash Biomedicine Discovery Institute. <https://www.monash.edu/discovery-institute/news-and-events/news/2018-articles/translating-colorectal-cancer-organoids-into-patient-care> (accessed 11 July 2023).

4.1.4 Onshore production of model components

The opportunity

Many components used in non-animal models face challenges arising from their poor characterisation, batch variability, and limited traceability. Additionally, with limited large-scale production of non-animal model components in Asia-Pacific and components produced within Australia typically prototyped on an ad-hoc basis, Australian organisations typically source components from international suppliers.

Onshore component production can provide benefits for sovereign capability. Increased domestic production of non-animal model components could alleviate susceptibility to international supply and price fluctuations, streamline Australia's R&D supply chain, and enable higher throughput in R&D for non-animal model capabilities and broader biomedical research. Onshore production can also present export opportunities after establishing sufficient scale. International stakeholders noted the benefits of proximity between organisations using models that require tissue samples and established component manufacturers to reduce transit risks such as preservation of tissue quality.

Three components were most identified by stakeholders as being valuable for onshore production:

- **Human-derived stem cells:** Human-derived stem cells (adult stem cells and iPSCs), are sought-after components for complex in vitro models such as organoids and organs-on-chips. However, those from genetically and phenotypically well-characterised donor pools are difficult to source. The variability of currently available donor cell lines increases development costs, as customers must test and characterise batches individually before using them in models.
- **Non-animal-derived media:** Currently available animal-derived media components face poor characterisation and batch variability challenges, particularly foetal bovine serum (FBS), a widespread input into cell culture media.
- **Hydrogels:** Hydrogels are a synthetic animal-free alternative to Matrigel (a common animal-derived cell culture matrix) with reduced batch variability.[90]

Producing all three component types onshore would create an opportunity to sell them in combination as model development kits. This opportunity would represent a unique, well-differentiated international and domestic market offering.

90 Curvello R, Alves D, Abud HE, Garnier G (2021) A thermo-responsive collagen-nanocellulose hydrogel for the growth of intestinal organoids. Materials science & engineering. C, Materials for biological applications 124, 112051; Curvello R, Kerr G, Micati DJ, Chan WH, Raghuwanshi VS, Rosenbluh J, Abud HE, Garnier G (2021) Engineered Plant-Based Nanocellulose Hydrogel for Small Intestinal Organoid Growth. Advanced Science 8(1), 2002135.

Why Australia?

Australia's strength in stem cells provides a strong foundation and competitive advantage for developing well-characterised adult stem cell-derived and iPSC-derived models. Stem cell technologies are advancing quickly within Australia, with service facilities such as the Stem Cell and Organoid Facility providing iPSC-derived organoids for pharmacology testing and evaluating advanced technologies such as gene therapies.[91]

Australia is a notable global producer of FBS. As non-animal models become increasingly commonplace globally, producing and exporting non-animal-derived media will reduce demand for FBS. Developing an alternative media production capability will help prepare Australia for the market's likely transition away from animal-derived inputs such as FBS.

Cell culture matrix material is not easily accessible in Australia. Matrigel, for instance, is not produced at scale domestically, causing a dependence on international Matrigel supply. While small-scale production of hydrogels is present in Australia,[92] increasing domestic production will reduce reliance on offshore Matrigel supply, prepare for the transition away from animal-derived inputs, and address issues associated with batch variability.

Finally, Australian companies have successfully established scaled production of important non-animal model components in Australia for domestic and export markets. One such example is Schott Minifab, described in Case Study 4.

CASE STUDY 4: Local in vitro component manufacturing

Schott Minifab is headquartered in Victoria and manufactures and exports millions of high-standard (ISO9001 and ISO13485 certified) components for in vitro use per year. Founded as Minifab in Melbourne in 2002, the organisation was acquired by Schott AG in 2019 due to the two organisations' complementary capabilities in polymers and glass components, leading to a broadened product range for their overlapping customer bases.

Schott Minifab partners with clients to customise and develop point-of-care cartridges, lab-on-a-chip solutions (including organ-on-chip) and other medical device components for in vitro use. Their capabilities include microfluidic design (fluids at the nanolitre scale), polymer-based material selection (for the precise movement of these fluids), prototyping, and advanced manufacturing processes for high volume production.[93] As of 2022, Schott Minifab is one of the world's largest contract manufacturers of microfluidic devices, with 12.6% of the market.[94]

91 Children's Medical Research Institute (2023) Stem Cell & Organoid Facility. <https://www.cmrijeansforgenes.org.au/research/research-facilities/scof> (accessed 11 July 2023).

92 Fatimi A (2021) Hydrogel-Based Bioinks for Three-Dimensional Bioprinting: Patent Analysis. Materials Proceedings 7(1), 3.

93 MTPConnect (2023) MiniFAB (Aust) Pty Ltd. <https://www.mtpconnect.org.au/Company?Action=Profile&Company_id=99> (accessed 11 July 2023); SCHOTT MINIFAB (2018) Diagnostics & life science product development & manufacture. <https://schott-minifab.com/what-we-do> (accessed 11 July 2023); SCHOTT MINIFAB (2019) SCHOTT AG to acquire Australian microfluidic expert MINIFAB. <https://schott-minifab.com/item/43-schott-ag-to-acquire-australian-microfluidic-expert-minifab> (accessed 11 July 2023).

94 Yole Intelligence (2022) Status of the Microfluidics Industry 2022. <https://yolegroup.com/articles/> (accessed 11 July 2023).

4.2 Recommendations

This section outlines ten recommendations that aim to provide Australia with the foundation for pursuing the four identified opportunities. Recommendations were co-developed with industry, research, and government stakeholders. While the opportunities were developed by considering what could be possible within a 15-year time horizon, setting Australia on a path towards these opportunities would require actioning all recommendations within five years.

Within these five years, recommendations can be prioritised and ordered by themes, with those aimed at coordinating and updating existing processes considered the most important first steps by those consulted (Figure 9). These activities would set a strong foundation for the remaining recommendations, which aim to integrate local capabilities into medical product development before strengthening production and commercialisation. Recommendations for non-animal model validation data will provide the evidence base to generate momentum across the other themes.

Consideration and implementation of the proposed recommendations would benefit from national coordination. The Australian Government would likely lead initial decision-making in these areas. However, many of the recommendations will require dedicated support and implementation from other levels of industry, research, and government.

While the design of these recommendations is to mature Australia's medical product development capabilities, implementation of these recommendations could also benefit applications in other fields such as veterinary and agricultural medicines, industrial chemicals, cosmetic testing, and eco-toxicology.

Figure 9. Recommendations for strategically maturing Australia's non-animal model capabilities

Coordinate and update existing processes

1. Establish a national consortium that coordinates and promotes Australia's non-animal model capabilities
2. Develop national data collection standards on the use of animals in scientific research, teaching and testing
3. Align TGA processes and industry guidance with new FDA procedures for accepting non-animal model data

Integrate local capabilities

4. Develop a national biobanking and tissue collection network
5. Integrate outputs from NCRIS platforms into a coordinated pipeline for non-animal models

Strengthen production and commercialisation

6. Facilitate IP management and material access for research and industry collaborations
7. Enhance commercial skillsets across the non-animal model sector
8. Update biomedical R&D infrastructure to support non-animal model capabilities

Validation data

9. Conduct retrospective studies that compare animal and non-animal model predictivity
10. Conduct systematic reviews of locally and internationally developed non-animal models

RECOMMENDATION 1

Establish a national consortium that coordinates and promotes Australia's non-animal model capabilities

The Australian non-animal model landscape has a breadth of expertise, primarily operating in siloes. Forming a consortium centred on Australian non-animal model capabilities and 3Rs advancement would strengthen existing integration initiatives, increase the chances of productive collaboration, and facilitate advocacy for local capabilities.

Consulted stakeholders identified existing entities that share some of these responsibilities in the broader Australian biomedical sector and could form the basis of the national consortium. These include the Australian & New Zealand Council for the Care of Animals in Research and Teaching (ANZCCART), CSIRO, MTPConnect, Phenomics Australia, the Therapeutic Goods Administration (TGA), and Therapeutic Innovation Australia.

Regardless of where specific responsibilities sit, strong collaboration with these existing organisations will be critical for the consortium's success. Adequate resourcing, both in terms of funding and dedicated personnel, will also be essential for the consortium to succeed. Exploring and identifying mechanisms that can support its establishment and sustainability over time should be initial priorities.

Stakeholders highlighted several activities that would benefit from being governed by the consortium:

- Supporting the establishment of networks of local developers, input producers, and prototyping groups to reduce manufacturing costs and encourage the formation of small-scale value chains.
- Fostering communication and collaboration between research, industry, government, and regulators, both domestically and internationally.
- Identifying, promoting, and facilitating partnerships of local institutions with multinational companies by matching their organ or disease modelling interests with locally developed models and expertise.
- Tracking key national non-animal model R&D and industry capabilities and promoting these domestically and abroad.
- Representing Australian interests at global non-animal model forums and existing international initiatives around global harmonisation, regulation, standards, and privacy. For example, the Putting Science into Standards projects with CEN-CENELEC or the Microphysiological Systems Affiliate of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ MPS).[95]
- Developing, maintaining, and promoting a publicly available resource that collates emerging funding opportunities (public and industry-led initiatives), both national and international, relevant to non-animal models and 3Rs advances.
- Building on reports such as this one, develop a national strategy that includes investment priorities, the coordination of efforts across Australian entities, and the broad analysis of global unmet needs. The EU's Smart Specialisation initiative represents a successful model to consider for national coordination, leveraging localised strengths and differences.[96]
- Facilitating the collaborative development of frameworks for locally developed models, including reporting requirements for research involving non-animal models, performance standards, validation requirements, qualification pathways, and steps for regulatory acceptance.
- Developing manufacturing standards, standardised protocols, and validated guidelines for model inputs and complete models to minimise the need for repetitive validation by end-users.

95 CEN-CENELEC (2023) Putting-Science-Into-Standards (PSIS). PSIS. <https://www.cencenelec.eu/get-involved/research-and-innovation/cen-and-cenelec-activities/putting-science-into-standards/> (accessed 11 July 2023); IQ Microphysiological Systems Affiliate (2019) About Us. IQ MPS. <https://www.iqmps.org/about-us> (accessed 11 July 2023).

96 European Commission – Joint Research Centre (2022) Smart Specialisation. EU Science Hub. <https://joint-research-centre.ec.europa.eu/scientific-activities-z/smart-specialisation_en> (accessed 11 July 2023).

RECOMMENDATION 2

Develop national data collection standards on the use of animals in scientific research, teaching, and testing

Data regarding the use of animals for scientific purposes is collected and shared in different forms by State and Territory governments and animal ethics committees in Australia. Most of this data lacks granularity around the specific research or activities, making it challenging to understand where and how animals are being used. Funding bodies, such as the NHMRC, have no role in the standardised collection or use of this data.

National data collection standards on the use of animals for scientific purposes, aligned to established international standards, will help to inform funding decisions better to support the 3Rs, track the impact of 3Rs initiatives, guide infrastructure development, rationalise animal use, and inform priority areas for non-animal model development.

The EU's ALURES database is one example of an international standard Australia may look to align with. Specific animal use information collected under this system includes:[97]

- The number and species of animals, their origins, and dates of use.
- Type of research (basic, translational, or regulatory) and relevant sub-categories.
- Purpose of research (biomedical or ecological/environmental purposes).
- Diseases, therapeutic areas, or organ systems being researched.

This activity would require a coordinating entity, which would be responsible for consulting with key research, industry, government, regulatory groups, and animal protection organisations across all jurisdictions. This entity would also need to develop standards, and data collection and reporting systems. Stakeholders suggested several existing organisations could be appropriate for this responsibility, including the Australian & New Zealand Council for the Care of Animals in Research and Teaching (ANZCCART), CSIRO or the Federal Government.

RECOMMENDATION 3

Align TGA processes and industry guidance with new FDA procedures for accepting non-animal model data

Stakeholders cited a lack of clarity on the acceptability of non-animal model data to fulfil regulatory requirements as a barrier to the greater adoption of non-animal models in medical product development. Leveraging new biological models and associated data to support medical product development will require more explicit guidance and formal regulatory precedents of non-animal model-assessed products.

Aligning Australia's national regulatory processes and guidance material with leading international jurisdictions with more advanced non-animal model ecosystems will provide researchers and industry with greater confidence to plan for the use of non-animal models. The FDA and the EMA are at the forefront of global efforts to integrate non-animal models into regulatory practice and represent important institutions for continuous engagement by the TGA. Aligning TGA processes with the FDA is proposed due to the US regulator's proactive role in collaborative programs that are continuously producing non-animal model improvements and guidance, as well as the extensive public funding provided to the sector in the US. Both are factors likely to spur faster regulatory innovation that the TGA can build upon.

Beyond the FDA and EMA, a joint effort between the TGA and other national regulators for producing harmonised guidance on non-animal model data acceptability could further facilitate the growth of non-animal model applications. Global harmonisation is a longer and more complex process than aligning to a single regulator, but it will encourage greater market access for Australian collaborations and commercial offerings in the long term.

While harmonisation activity is being explored, several short-term initiatives that clarify regulatory requirements could help prepare Australian stakeholders for the challenges and opportunities of greater regulatory alignment on non-animal models. These initiatives could include conducting reviews of non-animal model data

97 European Commission – Directorate-General for Environment (n.d.) Statistics and non-technical project summaries. Animals in science. <https://environment.ec.europa.eu/topics/chemicals/animals-science/statistics-and-non-technical-project-summaries_en> (accessed 11 July 2023).

98 Baran SW, Brown PC, Baudy AR, Fitzpatrick SC, Frantz C, Fullerton A, Gan J, Hardwick RN, Hillgren KM, Kopec AK, Liras JL, Mendrick DL, Nagao R, Proctor WR, Ramsden D, Ribeiro AJS, Stresser D, Sung KE, Sura R, Tetsuka K, Tomlinson L, Van Vleet T, Wagoner MP, Wang Q, Arslan SY, Yoder G, Ekert JE (2022) 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 39(2), 297–314.

acceptability across countries and actively participating in forums where the requirements for advanced non-animal models and the suitability of their data for regulatory purposes are being discussed. This includes attending the joint IQ MPS-FDA workshops with industry representatives and regulatory agencies and engaging the regulatory boards of dedicated organisations like EUROoCS.[98]

RECOMMENDATION 4

Develop a national biobanking and tissue collection network

Patient-derived cells and tissues are essential for the development of more biologically relevant models of disease that improve patient outcomes. A national biobanking and tissue collection network can provide researchers and industry access to well-characterised cells and tissues that support preclinical testing of therapeutic candidates and personalised models for clinical treatment selection.[99]

A national biobanking and tissue collection network could also facilitate a greater representation of the Australian population in medical product and non-animal model development through more extensive, geographically and ethnically diverse patient cohorts. Greater population representation will enable the earlier identification of potential adverse events and better-suited treatments for a broader range of patients. Individual nodes could exist across States and Territories that exchange and share methodologies, clinical practices, standard operating procedures, expertise, and data.

While Australia has the foundation to enable a national biobanking and tissue collection network – including existing biobanks – there is still a requirement for planning and coordinating contributing facilities and programs at the national level. A set of national patient registries, organised by therapeutic area, could offer an initial basis to build a national biobanking and tissue collection network. Registries provide a standardised format and integrate patient characteristics with therapeutic decisions, collected tissue data, and clinical outcomes.

Stakeholders noted that the network's set-up should consider the biobanking and tissue collection needs and integrate multiple discrete steps and participants into a streamlined pipeline. The needs include:

- Patient recruitment, support, retention, and follow-up, with assistance from nursing staff experienced in clinical trials.
- Sample collection, in coordination between clinicians and researchers for patient and tissue selection.
- Sample processing, derivation into stable in vitro models for longer-term storage, and standardised characterisation with strict data quality controls.
- Logistics for patient tissue delivery and access pathways to stored in vitro models for researchers.
- Large-scale digital infrastructure that allows secure data storage and sharing, monitoring tissue activity (e.g., transport, provision, use), and integrating de-identified clinical data to support future precision medicine applications.
- Research partnerships to enable access and uses by industry, which involves testing novel therapeutics on a range of patient-derived models and delivering the data to partnering companies.
- Coordinated ethics frameworks considering broad subsequent uses for the collected tissues from the start to support R&D activities and data generation.

99 Roth A (2021) Novel human cell models in drug development: How 3D, Organoids & Organs on Chips can improve and renew current paths – and our vision for the future. Danish 3R-symposium. <https://en.3rcenter.dk/fileadmin/user_upload/Editor/images/Om_Danmarks_3R-Center/Symposium/Symposium_2021/Adrian_Roth-Danish_3R-symposium_Nov_2021-_FINAL.pdf> (accessed 11 July 2023).

RECOMMENDATION 5

Integrate outputs from NCRIS platforms into a coordinated pipeline for non-animal models

High-quality biological model research outputs (e.g., biological materials, novel model types, human-relevant data, and hardware) are produced by multiple NCRIS platforms. However, a sequential process that supports the streamlined production of non-animal models is yet to connect them.

Increasing service coordination at the national level is supported by the formation of the NCRIS Health Group, comprising Bioplatforms Australia, the National Imaging Facility, Phenomics Australia, the Population Health Research Network, and Therapeutic Innovation Australia.[100] Their capabilities, in combination with those of other relevant NCRIS platforms like the Australian National Fabrication Facility (ANFF), could be explicitly integrated for non-animal model development, production and use. This approach would mirror the pipeline already established for novel therapeutics.

A holistic pipeline for non-animal model activity would use the outputs of one NCRIS platform as inputs for another, encouraging model standardisation, user-guided improvement, and increased uptake. A national pipeline builds upon the foundation set by the NCRIS Health Group, which could lead this initiative. The following discrete steps may help inform and advance the integration process:

- Identify all outputs relevant to non-animal models currently produced across the various NCRIS Health Group platforms and other platforms not yet aligned with NCRIS.
- Examine existing barriers to sharing and using platform outputs in an integrated, sequential process. These may include challenges or gaps in governance, funding, communication, ethics and privacy, or logistics.
- Propose specific outputs, models, and mature applications to support a small-scale pipeline. For instance, organ-on-chip production for trial pre-screening using ANFF-produced hardware and patient-specific iPSCs derived by members of the Phenomics Australia network.

RECOMMENDATION 6

Facilitate IP management and material access for research and industry collaborations

Variable IP management can represent a significant challenge for collaborative and fee-for-service work involving non-animal models.

A dedicated working group could co-design a streamlined, nationally coordinated framework that facilitates material transfer agreements between organisations, supports IP protections for outputs from non-animal model work in domestic and international markets, and allows sufficient clarity and flexibility for industry collaborations. The working group could include representatives from IP Australia, universities, medical research institutes, pathology labs and hospitals, industry organisations, funding bodies (e.g., NHMRC and ARC), and relevant professional associations like the Australasian Research Management Society.

100 Australian Government Department of Health and Aged Care (2023b) National Critical Research Infrastructure initiative. Our work. <https://www.health.gov.au/our-work/national-critical-research-infrastructure-initiative> (accessed 11 July 2023).

RECOMMENDATION 7

Enhance commercial skillsets across the non-animal model sector

Stakeholders described the limited commercial expertise of non-animal model researchers and developers, and a need for non-animal model expertise among commercial professionals nested within non-animal model developing organisations, as significant barriers to commercialisation in Australia. Skills and expertise necessary to improve commercialisation include business case development, economic modelling, capital raising, IP and sales, bench-to-bedside product translation, and biotechnology commercialisation leadership. Several initiatives could assist local organisations in addressing these skills gaps:

- Establishing knowledge transfer opportunities (e.g., secondments) for commercial professionals from local non-animal model developing organisations with leading international commercial non-animal model organisations.
- Recruiting experienced international biotechnology commercialisation specialists into key translational institutions.
- Providing commercialisation training to non-animal model researchers and developers. Such initiatives can draw from and build upon programs like Cicada Innovation's NSW Health Commercialisation Training Program.[101]

RECOMMENDATION 8

Update biomedical R&D infrastructure to support non-animal model capabilities

Enabling the broader use of non-animal models across the Australian medical product development process requires addressing infrastructure needs across fundamental research, translational research services, clinical applications, and manufacturing capabilities.

For instance, ensuring that equipment assessments at universities and research institutes are periodic and have a forward-looking approach that considers compatibility with complex in vitro models can further adoption in fundamental research. These assessments can help minimise long-term overreliance on animal and in vitro 2D models due to a lack of alternatives.

To fully enable the clinical applications of non-animal models, it will be essential to develop infrastructure near clinical settings for processing and using patient-derived tissues in personalised complex in vitro models. This proximity can help guarantee tissue viability and reduce testing timelines, making the process more compatible with clinical practice and needs.

Additionally, increasing the number of Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) accredited facilities can benefit the broader non-animal model ecosystem. Identifying high-quality settings within Australia and supporting their accreditation or re-accreditation can be an enabler of greater activity, particularly for organisations in the translational research services and manufacturing segments.

101 Cicada Innovations (2023) NSW Health Commercialisation Training Program. <https://www.cicadainnovations.com/nswhealthctp-updates> (accessed 11 July 2023).

RECOMMENDATION 9

Conduct retrospective studies that compare animal and non-animal model predictivity

The lack of direct performance comparisons regarding the predictivity of clinical outcomes has limited the uptake of non-animal models in regulatory toxicology testing.

Retrospectively applying non-animal models can provide valuable insights on several fronts. Assessing withdrawn medical products of known clinical toxicity can help benchmark non-animal to animal model predictivity performance (including species-specific differences). Similarly, a retrospective assessment of medical products that exhibited preclinical toxicity in animal models and did not advance to clinical trials can explore the loss of potentially useful medical products due to animal-specific toxicity that would not occur in humans. Both comparisons can encourage the adoption of non-animal models, help improve performance and usability, strengthen a knowledge base for regulators' future interpretation of data, and support a broader economic case linked to their use.

Moreover, conducting retrospective studies involving medical products of known toxicity could serve as the last evaluative step in the qualification and regulatory acceptance process of novel non-animal models.

RECOMMENDATION 10

Conduct systematic reviews of locally and internationally developed non-animal models

The many non-animal models already developed, locally and abroad, across different organ systems and for distinct applications represents both a significant challenge and an opportunity. Essential data that can inform the greater use of non-animal models throughout the medical product development process are available but require an objective, comprehensive and technical-oriented assessment. Conducting thorough systematic reviews of non-animal models and their documented uses in medical product development has been highlighted as a need by consulted stakeholders. Such reviews should:

- Assess models' capabilities, limitations, use aspects, and predictive performances. Comprehensive assessments should focus on the extent to which models replicate well-defined pathways or endpoints of human toxicity and disease.
- Cover different therapeutic areas and specific diseases with their respective clinically relevant endpoints.
- Where possible, support or integrate dedicated prospective or retrospective analyses, directly comparing predicted toxicity with clinical trial results.

Reviews are regarded as a cost-effective approach to assessing the field's current state, informing changes to local regulatory practice, identifying areas of unmet need, and further building support for the use of non-animal models in Australian research and industry. The EU Reference Laboratory for alternatives to animal testing (EURL ECVAM) has led comparable initiatives previously for seven disease areas.[102] An Australian project would benefit significantly from leveraging the work already done and engaging closely with EURL ECVAM. Systematic reviews could also identify suitable areas for Australian projects exploring the deliberate integration of non-animal models in medical product development, similar to the EU's overarching project on 'Innovations to accelerate vaccine development and manufacture (Inno4Vac)'.[103]

102 Disease areas include respiratory tract diseases, breast cancer, neurodegenerative disorders, immuno-oncology, immunogenicity testing for advanced medicinal therapy products, cardiovascular diseases, and autoimmune diseases. European Commission - Joint Research Centre (2022) Review of advanced non-animal models in biomedical research. Biomedical research. <https://joint-research-centre.ec.europa.eu/eu-reference-laboratory-alternatives-animal-testing-eurl-ecvam/biomedical-research_en> (accessed 12 July 2023).

103 European Vaccine Initiative (2023) Inno4Vac project. <https://www.inno4vac.eu> (accessed 11 July 2023); Innovative Medicines Initiative (IMI) (2021) Innovations to accelerate vaccine development and manufacture (Inno4Vac). Projects & results <http://www.imi.europa.eu/projects-results/project-factsheets/inno4vac> (accessed 11 July 2023).

4.3 R&D priorities

The recommendations outlined in the previous section will need to be supported by the research community's ongoing maturation and validation of non-animal models. For researchers seeking to contribute to these efforts, the priorities for advanced model development most frequently suggested by consulted stakeholders are presented below.

The specifics of these R&D activities will ultimately vary by model and tissue type. These priorities also represent areas of opportunity for novel commercial offerings or collaborations, given their status as unmet needs globally.

Support the economic case for non-animal models in medical product development

- Perform comprehensive economics studies that quantitatively assess non-animal models' direct and indirect economic benefits, including time and cost impacts across the entire product development process and broader impacts on patient safety and health outcomes.

Improve analytics for increasingly complex in vitro models

- Strengthen 3D model analysis capabilities by linking semi-automated testing, high-content imaging and read-out capture, and data processing pipelines.
- Implement detailed phenotyping technologies (e.g., single-cell RNA sequencing and live imaging) to characterise the temporal and spatial dynamics of cellular populations within models to assess the accuracy of tissue and disease modelling and the detailed effects of therapeutics.
- Embed real-time physicochemical and metabolite sensing capabilities in locally developed culture hardware to characterise culture microenvironments and assess cellular responses.
- Refine, validate, and implement data analyses powered by artificial intelligence approaches to leverage increasingly complex biological model outputs and clinical data for safety and efficacy assessments.

Advance the quality of model inputs and hardware

- Improve the design and composition of biomaterials used in in vitro 3D models to ensure maximum relevance to human physiology through appropriate signalling and biomechanical properties.
- Implement epithelial or endothelial barriers that use disease-relevant cell types and spatial arrangements instead of synthetic and non-physiological proxies.[104]
- Transition towards hardware materials that, unlike those currently used for prototyping, are optically clear, chemically inert, non-absorbent, and better-suited to large scale manufacture.
- Improve model designs (across hardware, biological inputs, and use protocols) to allow greater ease of use, manufacturing under strict QA and QC conditions, and off-the-shelf applications.
- Improve the design of the microfluidic chips used in organ-on-chip models to reach simultaneous culture, reproducibility, and output read-out levels compatible with high-throughput applications.
- Improve and standardise perfusion strategies, including vascular precursors or bioprinting, for in vitro 3D models that do not rely on external microfluidic systems (i.e., organoids and tissue explants). Enhanced perfusion is critical to increasing model size for better reflecting native tissue size and function.

Extend the capabilities of in vitro models for a closer recreation of human physiology across healthy and diseased states

- Optimise multi-organ modular culture approaches to enable physiologically relevant Absorption, Distribution, Metabolism and Excretion (ADME) studies, systemic toxicity, and pharmacokinetics/pharmacodynamics.
- Incorporate immune system interactions into in vitro models through optimised simultaneous culturing of immune cells, systemic distribution modelling, and replication of migration and tissue infiltration.
- Where relevant to the disease or condition of interest, extend the effective culture time of complex models to the multi-month range to reflect disease onset and progression and chronic and cumulative exposure effects.
- Optimise co-differentiation protocols to reduce variability in differentiation efficiency across batches, minimise unwanted cell phenotypes, and closely control the identity of cell populations in a model.
- Incorporate tissue-relevant biomechanical cues in complex models to support more comprehensive differentiation and maturation strategies.
- Deliberately integrate in silico modelling expertise at the outset of data-intensive biomedical research projects, such that the iteration between in silico and in vitro models leads to improvements in both.

104 Irrechukwu O, Yeager R, David R, Ekert J, Saravanakumar A, Choi CK (2023) Applications of microphysiological systems to disease models in the biopharmaceutical industry: Opportunities and challenges. ALTEX – Alternatives to animal experimentation 40(3), 485–518.

5 Appendices

A.1 Consulted stakeholders

CSIRO would like to thank the following organisations for their contributions to the project through interviews and reviews. The insights expressed throughout this report were developed by considering the collective views obtained alongside independent economic and qualitative research. They may not always align with the specific views of one of the consulted individuals or organisations. This list is not to be interpreted as an endorsement or promotion of this report.

23 Strands Pty Ltd	CSL Seqirus	Phenomics Australia
360biolabs	The Defence Science and Technology Group	QIMR Berghofer Medical Research Institute
ACT Health	European Commission Joint Research Centre (JRC)	Queensland Department of Agriculture and Fisheries
ARC Centre for Personalised Therapeutics Technologies (CPTT)	European Organ-on-Chip Society (EUROoCS)	Queensland Health
AusBiotech	Flinders University	Schott Minifab Pty Ltd
Australian & New Zealand Council for the Care of Animals in Research and Teaching (ANZCCART)	Gelomics Pty Ltd	Tessara Therapeutics Pty Ltd
Australian Clinical Trials Alliance	Griffith Institute for Drug Discovery (GRIDD)	The Australian National University
Australian Ethical	Harry Perkins Institute of Medical Research	The Medical Advances Without Animals Trust (MAWA)
Australian Government Department of Education	Humane Research Australia	The Peter Doherty Institute for Infection and Immunity
Australian Government Department of Health and Aged Care	Inventia Life Science Pty Ltd	The University of Adelaide
Australian Government Department of Industry, Science and Resources	Leiden University Medical Center	The University of Melbourne
Australian Government Office of the Chief Scientist	Medicines Development for Global Health	The University of Newcastle
Australian Organoid Facility	Melbourne Centre for Nanofabrication	The University of Sydney
Avicenna Alliance	Moderna	Therapeutic Goods Administration (TGA)
Bico	Monash Biomedicine Discovery Institute	Therapeutic Innovation Australia
BioMelbourne	Murdoch Children's Research Institute (MCRI)	Transport Canberra and City Services Directorate
Center for Alternatives to Animal Testing (CAAT)	National Health and Medical Research Council (NHMRC)	UK National Centre for the Replacement Refinement & Reduction of Animals in Research (NC3Rs)
Children's Cancer Institute	New South Wales Department of Primary Industries	University of South Australia
Children's Medical Research Institute	New South Wales Ministry of Health	US National Institutes of Health (NIH) – National Center for Advancing Translational Sciences (NCATS)
Cortical Labs Pte Ltd	OminiWell Pty Ltd	Victor Chang Cardiac Research Institute
Crux Biolabs Pty Ltd	Opthea	WA Health
Commonwealth Scientific and Industrial Research Organisation (CSIRO)	Peter MacCallum Cancer Centre	Walter and Eliza Hall Institute of Medical Research (WEHI)

QUALITATIVE SCALE	Capacity to perform comprehensively in a criterion, or requirements needed for use
Low	Limited capacity or limited requirements
Low-Medium	Minimal capacity or minimal requirements
Medium-High	Intermediate capacity or intermediate requirements
High	Significant capacity or significant requirements

A.2 Biological model comparisons

Table 6. Biological model comparisons[105]

	IN SILICO	IN VITRO				IN VIVO
QUALITATIVE CRITERIA		2D	3D	TISSUE EXPLANT	ORGAN-ON-CHIP (OoC)	ANIMAL MODELS
Biological resemblance **How close is the resemblance to the native process or tissue being modelled?**	**Low** Mathematical and probabilistic models focus on specific outcome prediction rather than the comprehensive replication of tissues and processes.	**Low** Conventional 2D cell cultures do not replicate tissue microenvironment architecture, composition, biomechanics, or the cellular dynamics they enable (e.g., migration and improved signalling).	**Low-Medium** Conventional 3D models are static, rely on matrices with limited human relevance, and face challenges in vascularisation and reproducibility (e.g., size, shape, and cell types present).	**High** Carefully sourced and cultured explants preserve relevant characteristics of tissues in vivo: diverse cellular populations, spatial arrangements, architecture, and complex interactions.	**Medium-High** Organ-on-chip devices enable continuous flow, controllable biomechanical cues, and multi-organ interaction but still require improvements for complex 3D architectures and reducing the use of extraneous materials.	**Medium-High** Animals are compatible with genetic modifications and transitory phenotype inductions capable of replicating human diseases. However, genetic, physiological, and behavioural differences persist, limiting model accuracy and result reproducibility.
Technical expertise **How much training is required for effective model use?**	**Medium-High** In silico models rely on knowledge and skills across chemistry, pharmacology, engineering, mathematics, cell biology and human physiology.	**Low** Cell cultures in a conventional 2D setting require limited training, core laboratory skills, and basic knowledge of cell biology.	**Low-Medium** In addition to the requirements for 2D cell culture, 3D models require more extensive knowledge of human physiology and materials engineering, plus training in the imaging and analysis of 3D cultures.	**High** Sourcing, preparing, and culturing human tissue explants requires skills (or interdisciplinary collaborations) across surgery, histology, anatomical pathology, and organotypic culture techniques.	**High** Organ-on-chip models leverage the skills described for conventional 3D models and require additional training in microfluidics and biomechanics.	**High** Using animal models requires specialised skills in animal husbandry, surgery, histology, and cell culture, and significant knowledge of pharmacology and a particular species' physiology.
Technological maturity **How close is the model to formal and widespread adoption of its evidence in regulatory submissions?**	**Medium-High** In silico models are well characterised and amenable to validation, with some variants (like quantitative structure-activity relationship models) already in regulatory use. However, more extensive human datasets could further optimise them.	**High** 2D models are widely accepted for specific regulatory applications (particularly chemical assessment) and are well-characterised and optimised.	**Medium-High** 3D models have well-established production methods, hardware compatible with existing equipment (e.g., plates) and are increasingly used for internal decision-making. However, better characterisation of cellular populations and inputs (e.g., matrices) is necessary to achieve the standardisation required for regulatory uses.	**Low** The high variability of primary tissues, the relative difficulty in sourcing them, and the lack of guidelines for their use in medical product development limit this model's maturity.	**Low-Medium** The technological maturity of organ-on-chip models is limited by the use of materials unsuitable for large-scale manufacture, the lack of minimum standards for commercially available platforms, and the still-unresolved formal validation and qualification of this model type for an initial context of use.	**High** The technological maturity of animal models is supported by extensive historical use, detailed characterisation, and prominence in regulatory applications.
Direct and indirect costs **When considering acquisition, associated costs and operational expenses, how comparatively expensive is the model?**	**Low** Once developed and trained (which can carry significant costs), model use is relatively inexpensive, limited to computational resource cost and result analysis.	**Low-Medium** Well-established practices, mass-produced consumables, existing economies of scale, and the limited expertise required minimise costs. First-time acquisition of the equipment can significantly increase the overall cost.	**Medium-High** 3D models maintain the same direct and indirect cost categories from 2D culture, with increases due to consumables (e.g., specialised plates, matrices, and growth factors) and more complex characterisation, imaging, and analysis.	**High** High expenses are associated with organotypic culture and with the use of primary tissue, which is likely to be surgically extracted, scarce and costly.	**High** Besides retaining the increased costs of 3D models, organ-on-chip devices require extensive supporting equipment (e.g., pumps), specialised consumables (e.g., microfluidic chips), and additional training for reliable use.	**High** Animal models involve direct expenses on husbandry, histology, and analysis, and indirect costs from extensive planning, preparation, and significant space demands.
Throughput **What is the model's capacity to test many experimental conditions and generate endpoint-relevant results in a short period of time?**	**High** Modelling an interaction or predicting an outcome is only limited by computational resources.	**High** 2D models are compatible with quick culture times, basic readouts, assay miniaturisation, and simple handling. This compatibility makes them amenable to standardisation, automation, and large-scale parallel culture, which are vital for high throughput.	**Medium-High** Due to their increased complexity, 3D models require longer production or culturing times (e.g., organoids) and specialised characterisation, output detection and analysis. However, they remain compatible with large-scale production, automation, and parallel testing.	**Low** The lower availability of primary tissues, short culture longevity and technical complexity of organotypic culture (often dependent on manual interventions or custom steps) limit the use of explants for large-scale, parallel testing.	**Low-Medium** Available organ-on-chip devices still need to improve in their throughput due to the extensive equipment required to operate individual chips (which precludes scalability) and the prevalent use of few wells/systems per chip (which limits parallelisation).	**Low** While one animal may be used to assess multiple distinct endpoints, it remains a single experimental unit. Animal models also rely on extensive manual labour and require longer overall timeframes to yield results (e.g., acclimation, testing, processing).

Notes: (i) 'in vitro 3D' includes scaffolds, spheroids, and organoids. (ii) There are significant differences between animal models (e.g., rodents vs primates).

105 Ekert JE, Deakyne J, Pribul-Allen P, Terry R, Schofield C, Jeong CG, Storey J, Mohamet L, Francis J, Naidoo A, Amador A, Klein J-L, Rowan W (2020) Recommended Guidelines for Developing, Qualifying, and Implementing Complex In Vitro Models (CIVMs) for Drug Discovery. SLAS Discovery 25(10), 1174–1190; Irrechukwu O, Yeager R, David R, Ekert J, Saravanakumar A, Choi CK (2023) Applications of microphysiological systems to disease models in the biopharmaceutical industry: Opportunities and challenges. ALTEX – Alternatives to animal experimentation 40(3), 485–518; Low LA, Mummery C, Berridge BR, Austin CP, Tagle DA (2021) Organs-on-chips: into the next decade. Nature Reviews Drug Discovery 20(5), 345–361.

A.3 National strengths analysis

Methodology

Table 7. Search methodology

RESEARCH QUESTION	DATA SOURCE	METHODS	ANALYSIS
Research strengths What non-animal models does Australian research have comparative global strengths in?	Web of Science (WoS) Core Collection	Bibliometric analysis via MeSH defined search term lists per non-animal model type and organ system (19/02/2018 – 19/02/2023).	**Metric:** Publication counts per organ system/non-animal model type combination (e.g., 3D-Nervous system), Australian percentage of global publications, and global ranking for Australia. Based on these metrics, combinations were deemed to be research strengths (Australian percentage of global publications > 3%).
Clinical strengths What condition categories does Australia conduct the most clinical trials in?	Australia and New Zealand Clinical Trials Registry (ANZCTR)	Search of condition categories that can be directly matched to an organ system (19/02/2018 – 19/02/2023)	**Metric:** Number of registered clinical trials, with recruitment in Australia, per condition category (e.g., neurological). Individual condition categories were sorted based on the absolute number of clinical trials for the period, with priority assigned to the top 5.
Industry strengths What therapeutic areas does Australian industry participate the most in?	AusBiotech Australian Life Sciences Innovation Directory	Search of primary therapeutic areas that can be directly matched to an organ system (as of 19 February 2023)	**Metric:** Number of companies operating in relevant primary therapeutic areas (e.g., Diseases of the nervous system/ neurology) The therapeutic areas AusBiotech-listed companies operate in were sorted based on the absolute number of companies, with priority assigned to the top 5.
National strengths: Areas of alignment that emerged after matching organ systems (research) to their equivalent condition categories (clinical) and therapeutic areas (industry).			

Model assumptions and limitations

- The research strengths component focuses on publication output by organ system, non-animal model type, and the combination of the two. No impact metrics were applied (e.g., category normalised citation impact) because of the small number of articles in some combinations. The focus on output supports a consistent approach across the different combinations and the comparison to other countries. However, it does not capture non-public R&D outputs: industry platforms, commercial-in-confidence work by research groups, and in-progress research. Commercially oriented data sources like patents were also out of scope.
- Absence of representation in the analysis results should not be interpreted as a lack of high-quality research occurring in an area or mature models that could evolve into commercial offerings.
- Despite the use of structured lists in the research strengths analysis, the output of each search contains a percentage of mismatched articles due to language overlap between non-animal model categories. Publication counts should be considered ‘likely hits’ instead of exact figures.
- Some of the examined organ system categories are not mutually exclusive between themselves (e.g., urogenital, and reproductive systems). They are analysed and presented individually despite their overlap to allow comparison to ANZCTR Condition Categories and Australian Life Sciences Innovation Directory Therapeutic Areas.

The analysis does not consider certain condition categories (clinical trial strengths) and primary therapeutic areas (industry strengths) as they cannot be directly matched to an organ system. Such is the case with cancer/neoplasms/oncology, as it represents a broad category encompassing all organ systems.

Summary of results

Table 8. Australian share of global publications by organ system and non-animal model type for combinations where national activity accounts for ≥3% of global output.

ORGAN SYSTEM	NON-ANIMAL MODEL TYPE	AU PERCENTAGE OF GLOBAL PUBLICATIONS	GLOBAL POSITION	GLOBAL TOTAL	AU TOTAL
Eye	3D (Scaffold and organoid)	7.5%	5	372	28
Urogenital system	3D (Scaffold and organoid)	6.2%	8	921	57
Reproductive system	3D (Scaffold and organoid)	6.1%	7	904	55
Eye	3D (General)	6.0%	6	599	36
Ear	Tissue explant	5.0%	8	40	2
Eye	2D	4.7%	6	610	29
Reproductive system	3D (General)	4.7%	8	2380	113
Urogenital system	3D (General)	4.7%	7	1779	83
Reproductive system	2D	4.6%	7	2073	96
Reproductive system	Tissue explant	4.6%	10	130	6
Cardiovascular system	3D (Scaffold and organoid)	4.5%	7	617	28
Respiratory system	2D	4.2%	10	1839	77
Urogenital system	2D	4.0%	6	1738	70
Nervous system	3D (Scaffold and organoid)	4.0%	10	1557	62
Cardiovascular system	3D (General)	3.7%	10	1401	52
Integumentary system	2D	3.6%	10	1030	37
Metabolic and endocrine systems	3D (Scaffold and organoid)	3.4%	11	1104	38
Nervous system	3D (General)	3.4%	12	2801	96

Table 9. Organ system-model type combinations not emerging as current globally comparative strengths in the publication analysis

ORGAN SYSTEM	NON-ANIMAL MODEL TYPE
Blood	2D, 3D (General, scaffold and organoid), Tissue explant, Organ-on-chip
Cardiovascular	2D, Tissue explant, Organ-on-chip
Digestive system	2D, 3D (General, scaffold and organoid), Tissue explant, Organ-on-chip
Ear	2D, 3D (General, scaffold and organoid), Organ-on-chip
Eye	Tissue explant, Organ-on-chip
Inflammatory disorders and immune system	2D, 3D (General, scaffold and organoid), Tissue explant, Organ-on-chip
Integumentary	3D (General, scaffold and organoid), Tissue explant, Organ-on-chip
Metabolic and endocrine	2D, 3D (General), Tissue explant, Organ-on-chip
Musculoskeletal	2D, 3D (General, scaffold and organoid), Tissue explant, Organ-on-chip
Nervous system	2D, Tissue explant, Organ-on-chip
Reproductive health and childbirth	Organ-on-chip
Respiratory	3D (General, scaffold and organoid), Tissue explant, Organ-on-chip
Urogenital	Tissue explant, Organ-on-chip

Table 10. Number of registered clinical trials per condition category (Top 5), with recruitment in Australia (2018–2023, as of 19/02/2023)

ANZCTR CONDITION CATEGORY	NUMBER OF REGISTERED TRIALS	PERCENTAGE OF TOTAL
Total	**9633**	**100.0%**
Neurological	1108	11.5%
Cardiovascular	893	9.3%
Respiratory	840	8.7%
Musculoskeletal	831	8.6%
Inflammatory disorders and immune system (immune)	695	7.2%

Table 11. Number of companies active in the top 5 therapeutic areas, operating in Australia in 2023 (as of 19/02/2023).

AUSBIOTECH PRIMARY THERAPEUTIC AREA	NUMBER OF COMPANIES	PERCENTAGE OF TOTAL
Total[106]	**359**	**100.0%**
Diseases of the nervous system / neurology	101	28.1%
Cardiovascular / cardiology	70	19.5%
Respiratory / pulmonology	66	18.4%
Endocrine, nutritional, and metabolic diseases / endocrinology	61	17.0%
Musculoskeletal system and connective tissue	57	15.9%

106 As some companies present in the Life Sciences Directory operate in more than one therapeutic area, percentages for individual areas do not add up to 100%.

A.4 Australian industry capability

The organisations and capabilities listed below provide an overview of the Australian non-animal model industry. Table 12 includes organisations offering mature non-animal model products or services within Australia. Table 13 includes organisations offering supporting or adjacent services (including CROs with non-animal model capabilities, HTS providers and component producers). These organisations were identified through online searches and consultations. As such, this may not be an exhaustive list of all relevant industry capability.

Table 12. Organisations with mature non-animal model product or service offerings

ORGANISATION NAME *Click for more information*	ORGANISATION TYPE	PRIMARY MEDICAL PRODUCT DEVELOPMENT STAGE	NON-ANIMAL MODEL	APPLICATION (ORGAN OR DISEASE)
23 Strands Pty Ltd NSW	Company	Clinical application	In silico In vitro 2D In vitro 3D	Cancer, heart, reproductive
CellBank Australia (Children's Medical Research Institute) NSW	Research institution	Various	In vitro 2D – iPSC, Cell lines	Various
Centenary Institute NSW	Research institution	Discovery development	In vitro 2D – iPSC and others In vitro 3D	Cancer, heart, respiratory, skeletal
Cortical Labs Pte Ltd VIC	Company	Various	In silico In vitro 2D	Brain
Griffith University, Griffith Institute for Drug Discovery [#] QLD	Research institution	Fundamental research, Discovery development (HTS), Preclinical development	In vitro 2D	Various
Harry Perkins Institute of Medical Research, Translational Cancer Research Program in Oncology [0] WA	Research institution	Preclinical development	In vitro 3D – Organoid	Cancer
Hunter Medical Research Institute NSW	Research institution	Various	In vitro 2D In vitro 3D – Organoid	Brain, cancer, immune system, reproductive, respiratory
Inventia Life Science Pty Ltd [#] NSW	Company	Fundamental research, Screening and lead optimisation (HTS), Preclinical development	In vitro 3D – Organoid	Brain, cancer, liver, lung, ovaries, prostate, skin, stem cell, others
Monash University, Monash Organoid Program & Monash Genome Modification Platform [0] VIC	Research institution	Screening and lead optimisation, Preclinical development	In vitro 3D – Organoid	Breast, colorectal, epithelial tissue, gastrointestinal
Murdoch Children's Research Institute, iPSC Derivation & Gene Editing Facility [0] VIC	Research institution	Discovery development	In vitro 2D – iPSC-derived	Various
OminiWell Pty Ltd SA	Company	Target identification, Toxicology	Organ-on-chip	Brain, breast, gut, blood vessels
QIMR Berghofer Medical Research Institute QLD	Research institution	Target identification, Toxicology	In vitro 2D In vitro 3D – Organoid	Brain, heart

ORGANISATION NAME *Click for more information*	ORGANISATION TYPE	PRIMARY MEDICAL PRODUCT DEVELOPMENT STAGE	NON-ANIMAL MODEL	APPLICATION (ORGAN OR DISEASE)
RewiredBio Pty Ltd NSW	Company	Target identification	In silico	Various
Stem Cell and Organoid Facility (Children's Medical Research Institute) NSW	Research institution	Preclinical development, Clinical development	In vitro 2D – iPSC-derived In vitro 3D – Organoid	Various
Tessara Therapeutics Pty Ltd VIC	Company	Target identification, Screening and lead optimisation, Preclinical development	In vitro 3D	Brain
The University of Melbourne, Faculty of Medicine, Dentistry and Health Sciences [0] VIC	Research institution	Target identification, Preclinical development	In vitro 2D In vitro 3D – Organoid Tissue explant	Cancer, central nervous system, ear, eye, gastrointestinal, respiratory, stem cell, others
The University of New South Wales NSW	Research institution	Preclinical development, Functional assays	In vitro 3D – Organoid, adult stem cell derived	Gut, lung, others
The University of Newcastle NSW	Research institution	Preclinical development	In vitro 3D Tissue explant	Cancer, heart, intestine, respiratory, reproductive, others
The University of Queensland, Australian Organoid Facility [#] QLD	Research institution	Screening and lead optimisation (HTS), Preclinical development	In vitro 3D – Organoid, adult stem cell- and iPSC-derived	Brain, blood, kidney, cancer, others
The University of Queensland, In vitro Genome Engineering and Disease Modelling Service [0] QLD	Research institution	Target identification, Preclinical development	In vitro 2D In vitro 3D – Organoid	Various
The University of South Australia, Centre for Cancer Biology SA	Research institution	Target identification, Screening and lead optimisation, Preclinical development	In vitro 2D – Cell lines Tissue explants	Brain cancer
The University of Sydney NSW	Research institution	Toxicology, Pharmacology	Organ-on-chip	Lung
Victor Chang Cardiac Research Institute [#0] NSW	Research institution	Screening and lead optimisation (HTS), Functional assays	In vitro 2D – iPSC-derived In vitro 3D – Organoid	Heart
Westmead Institute for Medical Research NSW	Research institution	Target identification, Screening and lead optimisation, Preclinical development	In vitro 2D – Cell lines In vitro 3D – Cell lines, Organoid Tissue explant	Breast, cancer, immune system, skin

Table 13. Supporting service providers for non-animal model production

ORGANISATION NAME *Click for more information*	ORGANISATION TYPE	SUPPORTING SERVICE	NON-ANIMAL MODEL	APPLICATION (ORGAN OR DISEASE)
360biolabs (Burnet Institute) VIC	CRO	Functional assays, Pharmacodynamics, Pharmacokinetics	In vitro 2D	Cancer, infectious disease, others
ANU Centre for Therapeutic Discovery [0] ACT	Research institution	HTS	In vitro 2D In vitro 3D	Various
Children's Cancer Institute Drug Discovery Centre NSW	Research institution	HTS	In vitro 2D In vitro 3D	Various
Codex Research NSW	Company	Component production	Components for in vitro 2D and 3D	Various
Crux Biolabs Pty Ltd VIC	CRO	Functional assays, Pharmacodynamics, Pharmacokinetics	In vitro 2D	Immunology, inflammation, others
Flinders University, Cell Screen SA SA	Research institution	HTS	In vitro 2D	Various
Gelomics Pty Ltd QLD	Company	Component production	Components for in vitro 3D	Cancer, endothelial, mesenchymal, hepatic, others
Griffith University, Griffith Institute for Drug Discovery [#] QLD	Research institution	HTS	In vitro 2D	Various
Inventia Life Science Pty Ltd [#] NSW	Company	HTS	In vitro 3D – Organoid	Brain, cancer, liver, lung, ovaries, prostate, skin, stem cell, others
Monash University, Monash Institute of Pharmaceutical Sciences, Centre for Drug Candidate Optimisation VIC	Research institution	HTS, Biopharmaceutics	In vitro 2D	Cancer, central nervous system disorders, cardiovascular disease, infectious disease, metabolic disease
National Drug Discovery Centre (Walter and Eliza Hall Institute of Medical Research) VIC	Research institution	HTS	In vitro 2D	Cancer, cardiovascular diseases, degenerative disorders
Schott Minifab Pty Ltd VIC	Company	Component production	Components for in vitro 2D, 3D and organ-on-chip	Various
The University of Queensland, Australian Organoid Facility [#] QLD	Research institution	HTS	In vitro 3D – Organoid, adult stem cell- and iPSC-derived	Brain, blood, kidney, cancer, others
The University of Wollongong, Translational Research Initiative for Cellular Engineering and Printing NSW	Research institution	Bioprinting	In vitro 3D	Blood, ear, eye
Victor Chang Cardiac Research Institute [#0] NSW	Research institution	HTS	In vitro 2D – iPSC-derived In vitro 3D – Organoid	Heart
Victorian Centre for Functional Genomics (Peter MacCallum Cancer Centre) [0] VIC	Research institution	HTS	In vitro 2D In vitro 3D Tissue explant	Anal, breast, colorectal, gastrointestinal, heart, ovarian, pancreas, prostate, stem cell
vivoPharm Pty Ltd VIC	CRO	Toxicology	In vitro 2D	Various

Notes: (i) 'Various' refers to technologies that can be applied across a broad range of organs and diseases or medical product development stages. (ii) 'Research institution' includes charities, not-for-profit organisations and universities. (iii) [#] = Provider of both non-animal model and supporting service. (iv) [0] = Phenomics Australia supported.

A.5 Economic analysis methodology

Market sizing approach

The 2040 global opportunity for organoids and organs-on-chips was modelled based on existing market reports. Australia's potential global market share in 2040 was calculated using estimates of Australia's current market share percentage. Potential headcount employment was also calculated. Insufficient data prevented the modelling of other non-animal model types.

Current estimate of global organoid and organ-on-chip market size and CAGR

Current estimates of the global market for organoids and organs-on-chips were based on revenue averages provided by market research reports published between 2019 and 2022. All revenue figures were converted and adjusted for inflation.[107] The global organoids market in 2022 is estimated at $1.62 billion,[108] while the global organ-on-chip market in 2022 is estimated at $0.11 billion.[109]

Forecasts of the global market size for organoids and organs-on-chips were also collected. The year 2026, within the forecast range of several market research reports, was chosen as the starting year for projections out to 2040. The global organoids market in 2026 is estimated to be $3.26 billion, while the global organ-on-chip market in 2026 is estimated to be $0.31 billion.[110]

Non-animal model market report sources estimate revenue to grow by an average of 17.4% in the organoids market and 29.4% in the organ-on-chip market.[111] The 2026 revenue estimates were projected to 2040 using the respective average growth rate, relying on the assumption that the average CAGR for these models are constant over the years up to 2040.

Market share captured by Australia by 2040

Australia's market share for these model types was estimated using the number of published non-animal model research articles related to each model type as a proxy.[112] The average percentage of global research articles published over ten years, between 2013 and 2022, for organoids and organs-on-chips involving Australian researchers or institutions were 4.1% and 2.7%, respectively. These market shares were assumed to be static over the years.

Headcount employment for these models in Australia by 2040

The ratio of wages to revenue for Australian scientific research services was used as a proxy to estimate the relationship between wages and revenue for both non-animal models.[113] Figures taken from an Australian industry report include forecasts out to 2028.[114] A ten-year average of the wages to revenue ratio from 2019 to 2028 was estimated to be 39.1%. Similarly, the average wage per worker in Australian scientific research services was used as a proxy for the average wages in the non-animal model sector. Average wages in the scientific research services are currently $101,300,[115] and the ten-year average growth rate of wages from 2019 to 2028 (0.9%) was calculated from the same industry report and used to forecast wages out to 2040. The wage/revenue ratio and average wage were then applied to the Australian 2040 market share to derive headcount employment.

107 ATO End of financial year rates: USD 1 = $0.69 for year ending Dec 2022; USD 1 = $0.75 for year ending Dec 2021; USD 1 = $0.69 for year ending Dec 2020; USD 1 = $0.72 for year ending Dec 2019; Figures were adjusted for inflation using ABS CPI: All groups, Index Numbers and Percentage Changes for March Quarter 2023.

108 Technavio (2022), Human Organoids Market by End-user and Geography - Forecast and Analysis 2022-2026; bccResearch (2022), Laboratory Animal Models, 3D Cultures and Organoids: Global Markets; Allied Market Research (2022), Organoids and Spheroids Market by Type, by Method, by End User: Global Opportunity Analysis and Industry Forecast, 2021-2031 Market; The Insight Partners (2021), Organoids Market Forecast to 2027 - COVID-19 Impact and Global Analysis By Type, Application, Source, and Geography; Markets and Markets (2020), Human Organoids Market by Product, Usability, Application, End-user - Global Forecast to 2025.

109 Allied Market Research (2022), Organ-on-Chip Market by Type: Global Opportunity Analysis and Industry Forecast, 2020-2030; Data Bridge Market Research (2022), Global Organ-On-Chip Market – Industry Trends and Forecast to 2029; bccResearch (2022), Organ-on-a-Chip: Global Markets; GMD Research (2021), Global Organ-on-Chip Market 2020-2030; Technavio (2022), Organs on Chips Market 2022-2026 by End-user and Geography – Forecast and Analysis 2022-2026; Yole Group (2019), Organs-On-Chips Market and Technology Landscape.

110 The average global forecasted market size for 2026 was calculated by extrapolating the closest market size figures to the year 2026.

111 Based on an average of the growth estimates provided in the cited market research reports.

112 Based on web of science search results using keywords 'organoid' and 'organoids' for number of published organoid articles and 'microphysiological systems', 'microphysiological system', 'organ-on-a-chip devices', 'organ on a chip devices', 'organ-on-a-chip device', 'organ chips', 'organ chip', 'organ-on-a-chip', 'organ on a chip', 'organ-on-a-chips', 'organoids-on-a-chip', 'organoids on a chip', and 'organoids-on-a-chips' for number of published organ-on-chip articles.

113 While the development, adoption and commercialisation of non-animal models requires a diversified workforce (from research scientists to industrial developers and manufacturers to IP experts) the proportion of labour demand for research scientists would likely be greater, at least in the short term.

114 IBISWorld (2022) M6910 Scientific Research Services in Australia Industry Report.

115 IBISWorld (2022) M6910 Scientific Research Services in Australia Industry Report.

Summary of reported results

Table 14 summarises the results of the market sizing approach. The global organoids market in 2022 was $1.62 billion and is expected to reach $30.91 billion by 2040, with a CAGR of 17.4%. Under current research output trends, estimates of this market result in **4,200 jobs** and **$1.28 billion** in revenue for Australia by 2040. By comparison, the organ-on-chip market is at an earlier phase of adoption. This has been valued at $110 million worldwide in 2022, projected at $11.48 billion by 2040 (29.4% CAGR). The potential share for Australia by 2040 is **$310 million** in revenue, with **1,000 jobs**.

Table 14. Summary of economic analysis results by non-animal model.

	ORGANOIDS	OOC
Potential global revenue by 2040	$30.91B	$11.48B
Potential Australian revenue by 2040	$1.28B	$0.31B
Potential Australian headcount employment by 2040	4,200 jobs	1,000 jobs

Case study approach

This case study aimed to get a sense of cost, time and animal-use differences between animal and non-animal models in preclinical testing.

Animal use differences

Marty et al. (2022) estimated the potential percentage reduction in the number of animals if an equivalent non-animal method is used instead of, or in complement with, an animal model for several OECD-approved toxicity tests.[116] The potential percentage reduction in the number of animals used depends on factors such as regulatory acceptance and the adequacy of the information provided by a non-animal method versus an animal model. Table 15 incorporates this data.

Cost differences

Using information from Marty et al. (2022), equivalent animal and in vitro tests were grouped and compared based on their prediction of the same toxicity category.[117] The cost data for these tests were then extracted from Meigs et al. (2018).[118] Only one in vitro and one animal test were then chosen for each category based on the lowest cost of each test. It was assumed that laboratory decision-makers could choose the most cost-effective option for the given category.

The costs, in Euros and assumed to be in the base year 2018, were converted to 2022.[119] There was no consideration of additional costs that might arise from repeating the experiment or introducing new endpoints or tested doses, as the magnitude of such costs can vary significantly and is dependent on the outcome of the primary experiment.

116 Marty MS, Andrus AK and Groff KA (2022) Animal metrics: Tracking contributions of new approach methods to reduced animal use. ALTEX – Alternatives to animal experimentation, 39(1), 95–112.

117 OECD TG 474 and OECD TG 475 were assumed to be equivalent during grouping.

118 Meigs L., Smirnova L, Rovida C, Leist, M and Hartung T (2018) Animal testing and its alternatives – the most important omics is economics. ALTEX – Alternatives to animal experimentation, 35(3), 275–305.

119 ATO End of financial year rates ending 30 June 2019: EUR 1 = $0.66 for year ending December 2018. Figures were adjusted for inflation using ABS CPI: All groups, Index Numbers and Percentage Changes for March Quarter 2023.

Time differences

Data on the duration of equivalent animal and non-animal studies were collected to determine possible time savings. Technical information provided by OECD Test Guidelines (TG) documents was used for this purpose.[120] To accurately compare the duration of both animal and non-animal models, the time taken to prepare for the tests,[121] the observation period[122] and any post-exposure procedure[123] up until data analysis and reporting were all considered. The maximum duration of the test within the range provided was assumed to be the duration of a test, in line with a conservative approach. For instance, in OECD Test no. 487, the treatment time is said to last 3 to 6 hours and 6 hours was assumed to be the duration of the treatment time. It is important to note that the estimated time duration data does not capture confirmatory tests in the case of animal models and repetition of the experiment in the case of non-animal models, as the decision to conduct them is uncertain and contingent on the results of the primary experiment.

Summary of reported results

Table 15 summarises the results of estimating cost, time and animal use differences of equivalent animal and non-animal models. Table 15 is an extended version of the table used in section 4.1.2 and provides additional case studies.

For instance, when comparing non-animal testing to animal testing for eye irritation in the table below, it is observed that the former incurs an additional cost of $1,000. However, this can be offset by significant time savings of around 21.8 days and a reduction 2.7 in animal use. In the case of mutagenicity, using a non-animal test will only partially replace the animal model. It cannot be said with certainty how this will impact the cost and duration of the animal test used.[124] In this case, animal reduction is estimated to be between 0 to 6.4.

120 OECD (2021) Test No. 405: In Vivo Eye Irritation/Serious Eye Damage; OECD (2020) Test No. 437: Bovine Corneal Opacity and Permeability Test Method; OECD (2015) Test No. 404: Acute Dermal Irritation/Corrosion; OECD (2015) Test No. 435: In Vitro Membrane Barrier Test Method for Skin Corrosion; OECD (2010) Test No. 429: Skin Sensitisation; OECD (2022a) Test No. 442C: In Chemico Skin Sensitisation; OECD (2022b) Test No. 442D: In Vitro Skin Sensitisation; OECD (2022c) Test No. 442E: In Vitro Skin Sensitisation; OECD (2016a) Test No. 475: Mammalian Bone Marrow Chromosomal Aberration Test; OECD (2016b) Test No. 487: In Vitro Mammalian Cell Micronucleus Test.

121 The preparation period for animal models involves examination of the animal or animal parts for quality control purposes, the acclimation period, and any additional procedures such as de-skinning the animal. For non-animal models, the preparation period refers to the pre-culturing of cells, equilibration period or pre-incubation period.

122 The observation period for animal studies refers to the time elapsed after administration of the test substance during which animals are observed for signs of toxicity. In non-animal models, this time period is often referred to as the incubation period, treatment time or exposure to the test chemical.

123 Post-exposure procedures are more common in non-animal models and refer to any steps taken after the observation period such as ‘post-immersion’, ‘post-incubation period’, ‘HPLC analysis time’ or ‘centrifugation and staining of cells’.

124 As a result, we cannot talk about cost and time savings in this case. The same applies for skin sensitisation.

Table 15. Comparison between OECD tests featuring equivalent animal and non-animal models for various toxicity endpoints, across cost, time, and animal use.[125]

TYPE OF TOXICITY	OECD TG	TEST TYPE	STUDY COST (AUD 2022)	TIME DURATION (DAYS)	POTENTIAL % REDUCTION IN ANIMALS USED BY USING EQUIVALENT NON-ANIMAL MODELS	NUMBER OF ANIMALS USED[126]	POTENTIAL NUMBER OF ANIMALS SAVED BY USING EQUIVALENT NON-ANIMAL MODELS[127]
ACUTE ENDPOINTS							
Eye irritation/corrosion							
Acute eye irritation	405	in vivo	2,000	22.0	N/A	2.7	N/A
Bovine corneal opacity and permeability test (BCOP)	437	in vitro	3,000	0.2	100%	N/A	2.7
Skin irritation/corrosion							
Acute dermal irritation/ corrosion	404	in vivo	2,000	15.0	N/A	2	N/A
Membrane barrier test method for skin corrosion	435	in vitro	4,100	0.2	100%	N/A	2
Skin sensitisation[128]							
Local lymph node assay	429	in vivo	7,100	11.0	N/A	16	N/A
Direct peptide reactivity assay (DPRA)	442C	in vitro	6,400	2.3	33% – 50%	N/A	5.28 – 8
ARE-Nrf2 luciferase LuSens test	442D	in vitro	6,300	3.1	33% – 50%	N/A	5.28 – 8
Human cell line activation test (h-CLAT)	442E	in vitro	11,700	4.1	33% – 50%	N/A	5.28 – 8
GENOTOXICITY ENDPOINTS							
Mutagenicity							
Mammalian bone marrow chromosomal aberration test	475	in vivo	105,600	19.0	N/A	64	N/A
Mammalian cell micronucleus test	487	in vitro	14,400	2.3	0 – 10%	N/A	0 – 6.4

125 Adapted from Marty et al. (2022); Meigs et al. (2018); CSIRO Futures calculations.

126 Data on the number of animals used was derived from Meigs et al. (2018).

127 The figures provided are only average estimates and are not rounded to a full number of potential animals saved.

128 In the case of skin sensitisation, the three non-animal model tests must be done in complement to benefit from 33% – 50% reduction in animal use. As a result, the total cost of using non-animal model approaches would be $24,400 and the duration of those tests will be around 9.5 days assuming that they are not done concurrently. It cannot be said with certainty how this will impact the cost and duration of the animal model test.

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