

From Innovation Oasis to Research Desert

How Price Controls Imperil American Medical Innovation and the Search for Cures



U.S. Chamber of Commerce
Global Innovation
Policy Center

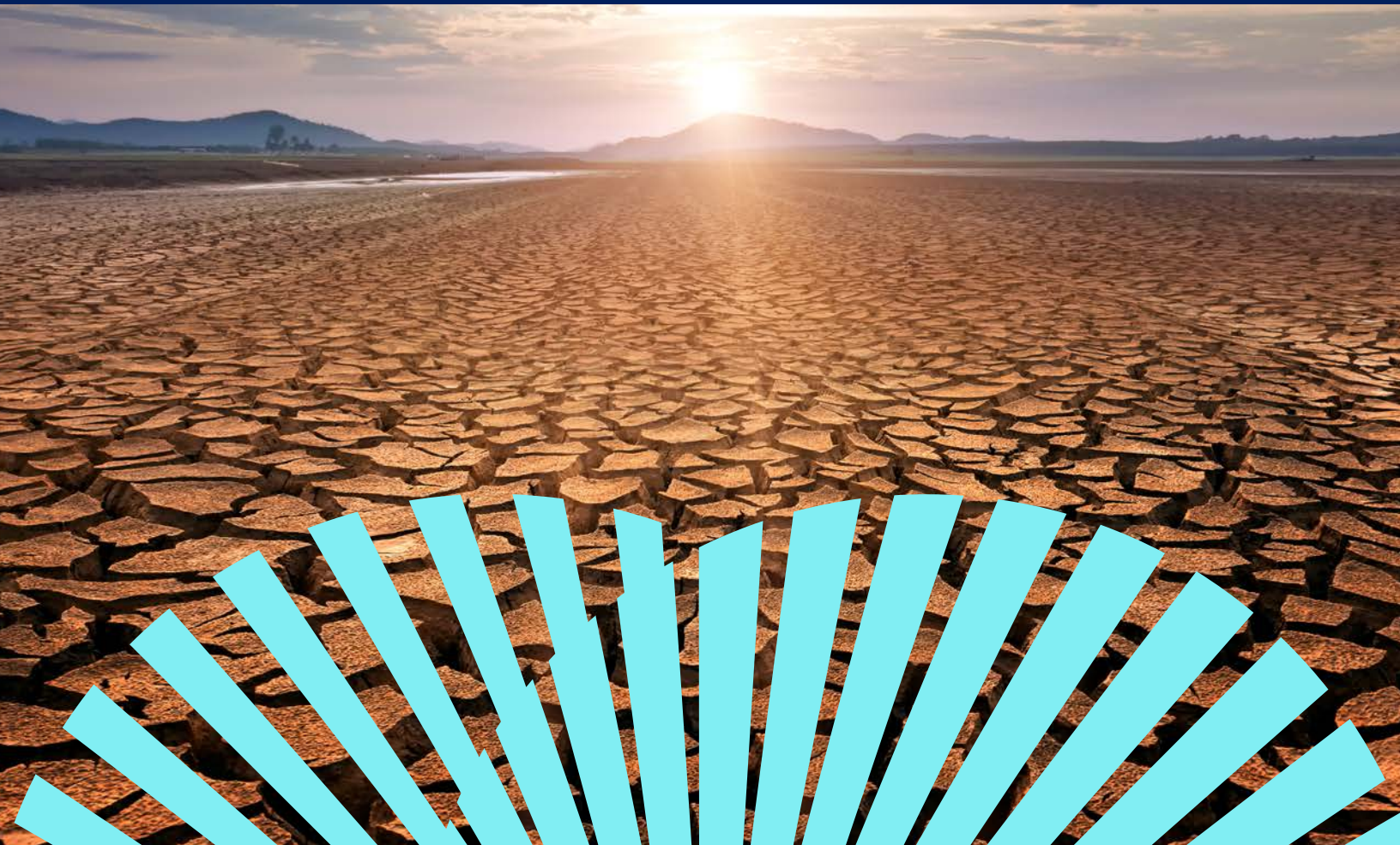


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Report Overview

This report investigates the imposition of national price controls and cost-containment measures on the biopharmaceutical sector and the Inflation Reduction Act's (IRA) potential direct and indirect negative long-term impacts on the most important part of the biopharmaceutical research and development ("R&D") process: clinical research and development. Clinical research is a cornerstone of the drug development process. Conducting clinical trials is part of an extensive process to determine which compounds out of hundreds under investigation may be further developed and eventually brought to market and in what manner. This report compares levels of clinical research between the United States and a sample of developed, major Organization for Economic Cooperation and Development ("OECD") economies that have historically imposed varying degrees of national price controls and cost-containment measures on the biopharmaceutical sector. Despite having many of the same scientific and technological strengths as the United States, rates of clinical research and biopharmaceutical innovation in these economies have consistently lagged the United States. As the experience of these economies strongly suggests, the imposition of national price controls

and cost-containment measures on the biopharmaceutical sector undermines many of the key incentives to invest and innovate in biopharmaceutical R&D.

The IRA is only the starting point for what will become a more comprehensive, draconian and regressive biopharmaceutical price controls. For example, initial IRA legislative proposals in 2022 had imposed a \$35 across-the-board price control on insulin in both public and private insurance markets.¹ The Biden administration's 2023 budget proposal also included the same extended \$35 price cap on insulin.² Additional proposals have been introduced in Congress that would impose the IRA's across the board price controls on the private insurance market. And the President has indicated he will campaign aggressively on expanding price controls on life saving medications. Altogether, the United States is on a trajectory similar to other OECD economics where the introduction of biopharmaceutical price controls and other cost and expenditure containment measures expand and evolve over time into more draconian and comprehensive policies. These policies cripple the free market and enterprise and, as this report demonstrates, cripple life saving innovation.

1. T Axelrod (2022) "Republicans strip \$35 insulin price cap from Democrats' bill -- but insist Senate rules are to blame", ABC News, August 8, 2022.
2. S Kimball (2023) "Biden budget would cap monthly insulin prices at \$35 for people with private insurance", CNBC, March 9, 2023.

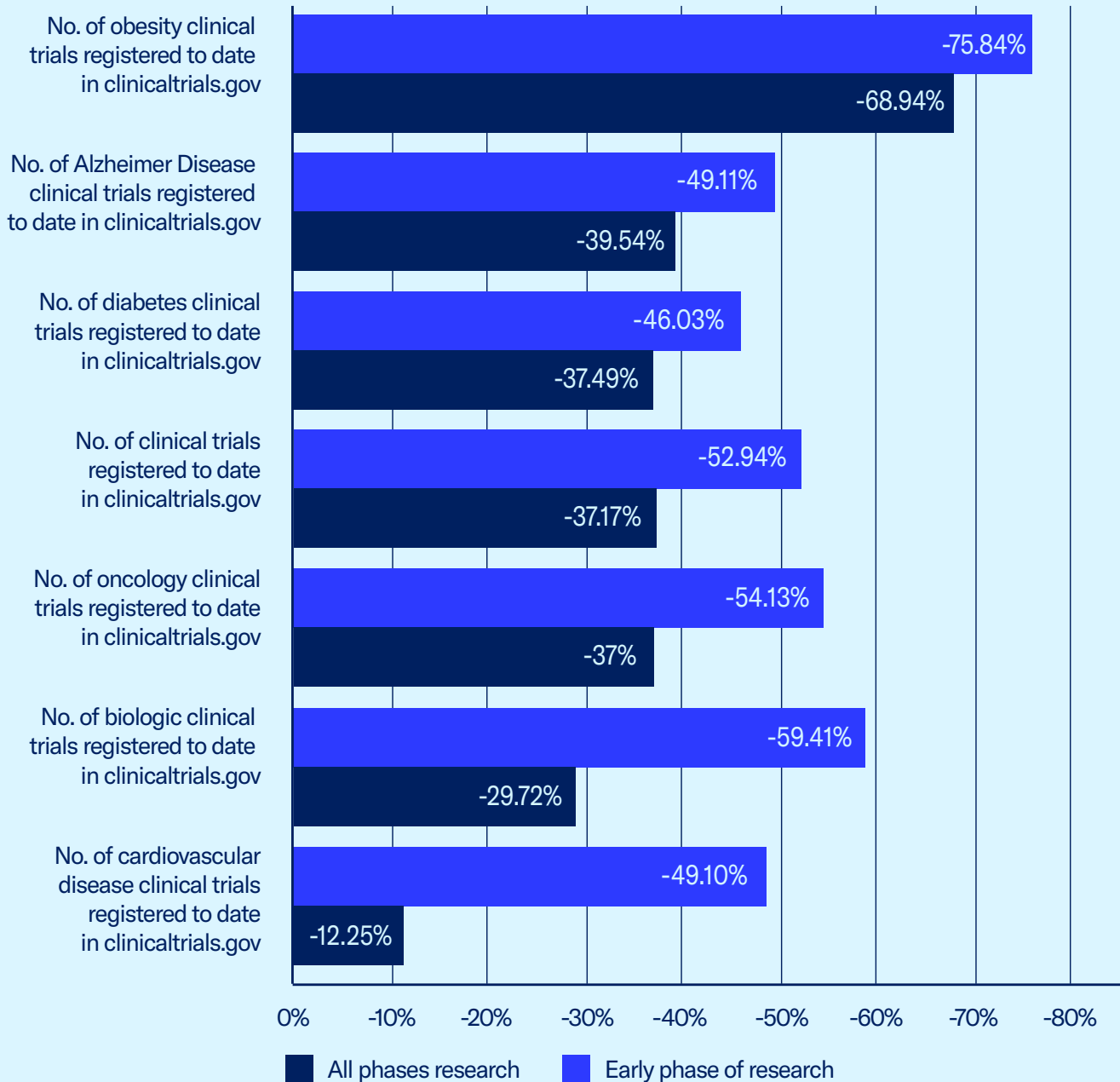
Headline Finding

Over time, the IRA and the expansion of national price controls and cost-containment measures on the biopharmaceutical sector in the United States is projected to both directly and indirectly reduce the number of clinical trials by thousands across all categories of research examined and by up to 75% in some therapeutic areas.

A decline in biopharmaceutical research and clinical trials activity in the United States to the sampled OECD average would result in a future reduction in all categories of clinical research analyzed. Depending on the therapeutic field, this reduction could amount to 12.25% (cardiovascular diseases) to 68.94% (obesity). For instance, trials related to future early-phase research risk being reduced by close to 50% or more. Specifically, early phase research related to biologics³ and cancer is projected to potentially be reduced by 59.41% and 54.13%, respectively. Early-phase research related to obesity could be reduced by more than 75%.

3. This category of research includes all therapeutic groups registered in clinicaltrials.gov. All other categories of research analyzed include both small-molecule and chemical-based products and large-molecule biological products.

Estimated Percentage Reduction for Clinical Trials in the United States



The Bottom Line: From World Leadership in Groundbreaking Innovation to the Emergence of Research Deserts—the IRA’s Negative Impact on Clinical Trials Activity in the United States.

As the data in this report show, the United States has historically been the global leader in all types of clinical research with particular strengths in areas of cutting-

edge, riskier, early-phase trials and research related to cancer, Alzheimer’s disease, diabetes, obesity, cardiovascular disease, and biologics. The IRA and the expansion of national price controls and cost-containment measures on the biopharmaceutical sector in the United States would jeopardize much of this research leadership and the future innovation that comes with it.

Introduction

A New Direction—the Introduction of Life Sciences Price Controls in the United States

Historically, the provision of health care in the United States has been based on a health insurance model principally managed via private funding and private delivery. Health care facilities—including hospitals and clinics—are mainly privately owned and operated. Similarly, the life sciences market has been predominantly market based. Private payers, including insurers, managed care organizations, and pharmaceutical benefit managers, aggregate various health plans and purchase life sciences on behalf of their members. Private payers often use formularies, differential cost sharing (including tiered copayments), and other methods to influence prescribing practices. In doing so, they can negotiate discounted prices from life sciences manufacturers and pharmacies. Individual hospitals and other health care institutions are also increasingly using formularies to manage costs.

Unlike many other high-income OECD economies, the U.S. federal government has not historically imposed national price controls or other restrictions and market access barriers on health technologies, including life sciences and medical devices. This has now changed with the passage of the IRA, which marks a sharp departure in U.S. health and life sciences policy. The law includes a series of fundamental changes to the pricing framework for medicines

covered under Medicare Part B and Part D. Presented as a way of granting the Department of Health and Human Services and the Centers for Medicare and Medicaid Services a greater ability to negotiate the price of a set number of medicines without generic or biosimilar competition that are covered under Medicare, the law grants such sweeping powers to the Secretary of Health and Human Services. It imposes punitive damages on manufacturers that fail to agree or abide by the price-setting mechanism, that it is a de facto expenditure and price control. The legislation uses the nonfederal average manufacturer price available for a given medicine based on the percentage increase in the consumer price index as the basis for the government-set price. Through a convoluted process, the so-called maximum fair price established for negotiated products must be equal to or less than what is termed a “ceiling price.” This ceiling price is a set percentage for each product (75%, 65%, or 40%) depending on how long a given product has been on the market with the lowest percentages applying to the oldest products. Furthermore, the IRA distinguishes between small- and large-molecule products with small-molecule entities subject to negotiations at a much earlier date. Although the IRA excludes certain orphan disease treatments from negotiations, this exclusion is narrow and

applies only to products used exclusively to treat one condition or disease. The legislation also sets the price of insulin at \$35 for all patients covered under Medicare. At the time of research, the Department of Health and Human Services and the Centers for Medicare and Medicaid were in the process of finalizing implementing regulations with an initial guidance

document issued in March 2023 and a revised document published in June⁴. In late August 2023, the administration released the list of 10 initial medicines subject to these new powers and price control measures.

Fewer Innovative Medicines and Longer Wait Times: The Direct Cost of Price Controls and Life Sciences Cost-Containment Policies

Many health care systems around the world have in place either direct or indirect mechanisms for regulating and adjusting the pricing and reimbursement of medicines. In many OECD economies, this is done directly through the imposition of price controls and other cost and expenditure containment measures as well as pricing and reimbursement negotiations between health ministries or government agencies and life sciences manufacturers. Prices and access to new and existing life sciences products are often determined through complicated formulas of internal and external reference pricing that compare the cost of medicines in a basket of economies. Many health systems have also adopted advanced systems of pharmacoeconomic and cost-effectiveness analysis and comparisons. Such systems provide a theoretical basis for rewarding innovation, therapeutic value, and advances in pharmaceutical treatment with a pricing premium. For example, in France, all innovative medicines that have received marketing approval must undergo

a pharmacoeconomic and health technology assessment (HTA) evaluation. Within this evaluation, the health authorities examine the extent to which the assessed product provides an improvement in actual clinical benefit (Amélioration du service médical rendu). Products that show a “major clinical improvement” can be awarded with an innovation premium. Similarly, in Germany, innovation price premiums are available for products that receive the highest therapeutic benefit assessment. In contrast, the IRA focuses almost exclusively on expenditure reduction regardless of a given product’s therapeutic value. Furthermore, the IRA grants such sweeping powers to the Secretary of Health and Human Services and imposes such punitive damages on manufacturers that fail to agree or abide by the price-setting mechanism that it does not in any way, shape, or form constitute a negotiation. Instead, the law is simply a de facto expenditure and price control mechanism. Similarly, the IRA purports to outlaw manufacturers’ ability to challenge

4. CMS (2023). “Medicare Drug Price Negotiation Program: Initial Memorandum, Implementation of Sections 1191–1198 of the Social Security Act for Initial Price Applicability Year 2026, and Solicitation of Comments,” March 15, 2023, Washington, DC.

major components of the program, eliminating administrative and judicial review of certain key decisions relating to the selection of products subject to price controls, the determination of maximum fair prices, and the determination of which medicines will be subject to “negotiations” and “renegotiations.” It is more likely than not that the current iteration of the IRA is only the starting point for what will become a more comprehensive and draconian system of biopharmaceutical cost and expenditure controls. For example, initial IRA legislative proposals in 2022 had imposed a \$35 across-the-board price control on insulin in both public and private insurance markets⁵. The Biden administration’s 2023 budget proposal also included the same extended \$35 price cap on insulin⁶.

That is also the trajectory in many other OECD economies where the introduction of biopharmaceutical price controls and other cost and expenditure containment measures over time evolve into more draconian policies.

Although varying considerably in scope and design from health system to health system, at heart, these policies impose a fundamental market access barrier and have a real and negative impact on the availability of new, innovative medicines and medical technologies. The historical evidence shows a clear and distinct disparity between economies with market access and regulatory environments that seek to strike a balance between maintaining financial stability and rewarding innovation and more

restrictive economies that prioritize cost control⁷.

Similarly, the most recent life sciences launch and product availability data show how economies with price controls and a more challenging life sciences market access environment consistently see substantially lower levels of product penetration and drug availability for patients. In fact, a large—and growing—disparity exists in product launches and market availability of new medicines between the United States and other advanced OECD member states with a history of price controls and life sciences cost-containment policies in place. For example, evidence collected by IQVIA on the availability of new medicines launched in the period 2012 to 2021 and published by Pharmaceutical Research and Manufacturers of America (PhRMA) in 2023 shows that many new health technologies and medicines are never launched in economies with strict price controls and life sciences cost-containment policies in place⁸.

This is a critical takeaway when examining the direct cost of introducing price controls and life sciences cost-containment policies. Many new products and medical innovations never make it into the market. This disparity between the United States and other developed OECD economies is even more pronounced when looking at specific therapeutic areas. For instance, the most recent data on the launch of new cancer medicines echo these broader findings and show how even Germany and the United

5. T Axelrod (2022) “Republicans strip \$35 insulin price cap from Democrats’ bill -- but insist Senate rules are to blame”, ABC News, August 8, 2022.
6. S Kimball (2023) “Biden budget would cap monthly insulin prices at \$35 for people with private insurance”, CNBC, March 9, 2023.
7. The academic literature on this is quite uniform in its findings. See, for example, Danzon, P. M., and Epstein, A. J. Effects of regulation on drug launch and pricing in interdependent markets, National Bureau of Economic Research, May 2008; and Kyle, M. Pharmaceutical price controls and entry strategies, Review of Economics and Statistics, Vol. 89, No. 1, February 2007, 88–99.
8. PhRMA (2023). “Global Access to New Medicines Report,” slide presentation, April 2023, Washington, DC, slide 11, “Percentage of New Medicines Launched by G20 Country (of all 460 new medicines launched from 2012 to end of 2021).”

Kingdom, which in the past have been the closest, are falling behind the United States⁹. This report shows that of 104 new products launched globally since 2017, 80% were launched in the United States, but only 56% were launched in Germany, France, Italy, and the United Kingdom.

In addition to seeing fewer product launches, patients in economies with national price controls and cost-containment policies in place also tend to wait longer to access new medicines in their respective national health systems. For example, patients in Europe's largest economies must wait almost a year or more before they can access new medicines, according to the European Federation of Pharmaceutical Industries and Associations' and IQVIA's annual "Patients W.A.I.T. (Waiting to Access Innovative Therapies)" survey. This survey measures the rate of availability and patient access to new and innovative medicines in Europe¹⁰. Long delays are pronounced in France and Spain where patients, on average, wait between 5 and 600 days.

Many national payers have an elaborate evaluation to determine whether a product should be included on a given formulary and the rate of reimbursement. Such evaluations restrict access to their respective national health systems through reimbursement limits, health technology and cost-effectiveness assessments, and reference pricing. Europe, France, Italy, Germany, Spain, and the United Kingdom all make use of such tools, as do Australia, Canada, Japan, and South Korea. There can be a long lag between market authorization—that is,

the date by which a new product is approved by drug regulators for use—and inclusion for public reimbursement. As mentioned previously, this is the case in most European economies and in Canada and Australia. For instance, in Australia, a 2018 study found that only 46% of all medicines registered in Australia between 2012 and 2017 were reimbursed (with a similar share for first-in-class medicines)¹¹. On average, the reimbursement evaluation for the products studied took 426 days, considerably longer than the OECD average for this period. The results are similar in Canada. For example, a 2016 report conducted by IMS Health Canada for Innovative Medicines Canada shows how Canadian patients have access to fewer innovative treatments than do other OECD economies¹². The study finds that long lags exist between market authorization and inclusion for public reimbursement. On average, for the period studied (2010–2014), it took 449 days from market authorization to reimbursement. For health systems that are predominantly publicly funded and organized, the latter date determines when most patients can access a new product, not the market authorization date. As these examples illustrate, it is not unusual for these delays to amount to several years of patients waiting for access to new products and technologies and to affect key therapeutic areas such as cancer medicines.

9. IQVIA Institute for Human Data Science (2022). Global Oncology Trends 2022, Outlook to 2026, May 2022, IQVIA, p. 7.

10. M. Newton et al. (2023). "EFPIA Patients W.A.I.T. Indicator 2022 Survey," EFPIA & IQVIA, April 2023.

11. Medicines Australia, Comparison of Access and Reimbursement Environments, Edition 4, 2018.

12. Innovative Medicines Canada & IMS Health Canada (2016), Access to New Medicines in Public Drug Plans: Canada and Comparable Countries, 2016 Annual Report, p. 5.

Less Revenue for Life Sciences Research = Fewer Resources for R&D for both the Public and Private Sector and Fewer New Medicines

The price controls included in the IRA are likely to have the same direct and indirect negative impact in the United States over time. Fewer medicines will be introduced into the market, and patients will need to wait longer to gain access to the latest lifesaving and life-altering life sciences innovations. These are direct consequences. But there is also likely to be sustained direct and indirect negative impacts on rates of R&D expenditure and, consequently, long-term rates of life sciences innovation and access to new forms of treatments.

The research and innovation that make the development of new life sciences products and technologies possible do not take place in a vacuum. They require a complex ecosystem of incentives and enabling policies at both macro and micro levels. These range from the institutional and ecosystem level—such as levels of tertiary education, technical skill, and intellectual property rights environment—to the more life sciences specific. The latter includes what type of life sciences and biotechnology R&D infrastructure an economy has in place, the availability of technology transfer laws and mechanisms, and the commercial environment for life sciences-based products and technologies, including medicines. Within this ecosystem, market and commercial incentives are critical factors in determining the extent to which both private and public sector entities can continue to invest in R&D and develop new life sciences products and health technologies together.

“[Bayh-Dole]...The most inspired piece of legislation to be enacted in America in the last half-century”¹³

In the mid-1980s the U.S. Congress passed two path-breaking pieces of legislation: the Patent and Trademark Law Amendments Act of 1984 and 1986 (the Bayh-Dole Act) and the Stevenson-Wydler Technology Innovation Act, which was later amended by the Federal Technology Transfer Act of 1986 and the Technology Transfer Commercialization Act in 2003. This legislation attempted to supply federal laboratories (including the National Institute of Health, NIH) and universities using federal funds with the incentives needed to work with industry for the purpose of translating early-stage research into usable products in the marketplace for the benefit of the wider public. The legislation sought to secure the above goals through three major changes to the intellectual property (IP) system. First, they allowed universities and federally funded bodies to retain ownership of the proprietary knowledge stemming from the research and daily activities of these institutions, including the ability to own patents on their inventions. Second, they encouraged these institutions to become much more proactive and professional in the management and exploitation of their IPRs by creating professional technology transfer offices. Finally, the legislation sought to stimulate the commercial and financial aspects of public-private collaboration, with the intention of creating new businesses (such as spin-off

13. The Economist (2002), “Innovation’s Golden Goose”, Technology Quarterly Section, p. 3. December 14, 2002

companies) and generating income for the institutions, as well as for the researchers¹⁴.

The importance of the Bayh Dole framework to U.S. innovation – and especially for the life sciences sector – cannot be overstated. The above quote from the *Economist* aptly sums up the positive impact the legislation had, and continues to have, on innovation in the U.S. Looking at general rates of innovation and commercialization activities this can be seen in terms of both patenting activity and actual economic impact and output. To begin with academic research into the effects of the Bayh-Dole framework have found a significant correlation between increased patenting activities at US universities and the Act. For example, a 2004 study found that university share of total patenting in the US increased from 0.69% of total patents at the time of legislation to just under 5% in 1996. Moreover, in a range of 117 industries (including biopharmaceuticals) the increase was from a decrease of 87% in 1969 to an increase of 1,648% in 1996¹⁵. The positive impact of Bayh Dole can also be seen in terms of direct and significant contributions to economic output and employment. For instance, using twenty-five years of data from the annual AUTM survey a 2022 study estimating the economic contribution of licensing activity by academic institutions found that in the U.S. the contribution of academic licensing to gross industry output ranged from USD631 billion to USD 1.9 trillion (measured in 2012 USD).¹⁶ Contributions to GDP were equally significant estimated at between USD 333 billion to USD 1 trillion

(measured in 2012 USD).¹⁷ In addition, this study found that this licensing activity was also a major contributor to the American jobs market, responsible for between 2.356 million-6.499 million person years of employment over the time period studied.

Perhaps the most telling statistic is the strong growth in industry-university collaboration and the, in effect, institutionalization of this partnership as the foundation of modern drug development. New technologies and research insights generated at universities and within public research are very seldom finished medical products ready to be commercialized. Instead, it often takes years of translational research and development by industry and biopharmaceutical manufacturers to take these technologies and generate a safe and effective medical product. For example, a decade after Bayh-Dole was passed the combined campuses of the University of California became the top recipient in the U.S. of biotechnology patents; a position formally held by Merck.¹⁸ Similarly, looking at licensing income for U.S. universities, not only has this grown exponentially since the mid-1980s but the life sciences sector is the predominant source of this income. For example, *Nature Biotechnology* in 2013 examined licensing income and sector-specific sources of this income for top U.S. universities and research institutes and found that of the USD1billion in total gross licensing income in 2013, over USD977million (97%) came from the life sciences sector.¹⁹ The number was similar with regards to

14. V. Loise & A.J. Stevens (2010). "The Bayh-Dole Act Turns 30", Les Nouvelles, December 2010, pp. 185-186, http://www.bu.edu/otd/files/2011/02/The_Bayh-Dole_Act_Turns_30.pdf.

15. Shane, S. (2004), "Encouraging university entrepreneurship? The effect of the Bayh-Dole Act on university patenting in the United States", *Journal of Business Venturing*, 19, pp. 127-151. See introduction to this article for a full discussion of the academic debate over the effects of Bayh-Dole.

16. L Pressman et al (2022), *The Economic Contribution of University/Nonprofit Inventions in the United States: 1996-2020*, BIO 2022, p. 3.

17. Ibid.

18. USPTO, (2006), *Technology Profile Report: Patenting Examining Technology Center Groups 1630-1660*, Biotechnology, Washington, 2006

19. B Huggett (2014) "Top US universities and institutes for life sciences in 2013", *Nature Biotechnology*, Volume 32 No 11 November 2014.



the number of start-ups and licenses executed with the vast majority being in the life sciences sector. More recent data paints a similar picture. Findings from the AUTM survey cited above shows that the vast majority – about 80% – of licensing income to universities and non-profit institutions, including research hospitals, is derived from the life sciences.²⁰ Perhaps the most noteworthy example is the USD 750 million in licensing income the University of Pennsylvania has received through the research of Katalin Karikó and Drew Weissman on the use of mRNA technology in vaccines.²¹

In the United States, one of the strongest drivers of life sciences innovation and this long-standing partnership between academic institutions, public research organizations and the private sector, has historically been the existence of a relatively free market in the pricing and sale of new medicines and life sciences technologies.

What direct and indirect impacts will the IRA have on this ecosystem and future levels of R&D and innovation?

Report Objectives

This report investigates the imposition of national price controls and cost-containment measures on the biopharmaceutical sector and the Inflation Reduction Act's (IRA) potential direct and indirect negative long-term impacts on the most important part of the biopharmaceutical research and development ("R&D") process: clinical research and development.

Clinical trials represent one of the most important activities carried out by life sciences research entities, whether private or public. Clinical research is a cornerstone of the drug development process. Conducting clinical trials is part of an extensive process for determining which compounds out of hundreds under investigation may be further developed and eventually brought to market and in what manner. The main purpose of clinical trials is to test and

provide proof of the safety, quality, and efficacy of new medicines or new uses, forms, or dosages of existing medicines.

The United States has historically been the global leader in all types of clinical research and accounts for more than one-third of the total number of clinical trials conducted or currently taking place globally. More importantly, in areas of cutting-edge, riskier early-phase trials and research related to cancer, Alzheimer's disease, diabetes, obesity, and biologics, the United States has accounted for an even larger proportion of clinical research.

This report compares levels of clinical research between the United States and a sample of developed, major OECD economies that have historically imposed varying degrees of national price controls

20. L. Pressman et al (2022), pp. 11-12.

21. N Pallas (2022) "Penn researchers receive royalties of \$750 million for breakthrough vaccine development", The Daily Pennsylvanian, June 23, 2022.



and cost-containment measures on the life sciences sector. These comparator economies are Australia, Canada, France, Germany, Italy, Japan, South Korea, Spain, and the United Kingdom. It is instructive that, despite having many of the same scientific and technological strengths as the United States, rates of clinical research and life sciences innovation in these economies have consistently lagged the United States.

As the experience of these economies strongly suggests, the imposition of national price controls and cost-containment measures on the life sciences sector undermines many of the key incentives to invest and innovate in life sciences R&D.

By comparing historical levels of clinical research between these economies and that of the United States, it is possible to estimate and project the direct and indirect negative impacts that the IRA is likely to have over time, not only in aggregate levels of life sciences R&D and clinical research but also in individual research areas.

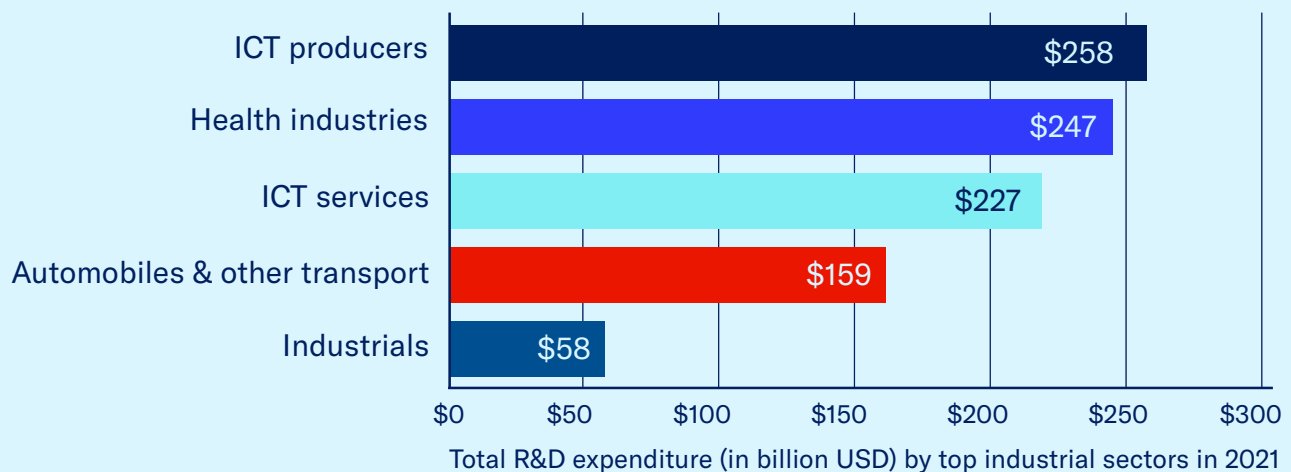
Clinical Trials and the Life Sciences R&D Ecosystem

The Basics of Life Sciences R&D

The life sciences sector is one of the most R&D-intensive sectors in the world. In 2019, Deloitte estimated global life sciences R&D spending to be around \$177 billion.²² A substantial proportion of this expenditure comes from members of the PhRMA trade association. Comparable data related to 2019 are available from PhRMA's annual 2020 membership survey. Here PhRMA estimated that R&D expenditure by member companies in 2019 totaled more than \$83 billion.²³ In other words, R&D spending by PhRMA member companies accounted for almost half of total expenditures in 2019.

Indeed, compared with other parts of the economy and industrial sectors, the research-based life sciences industry invests significantly more in R&D in absolute terms and as a percentage of sales. Figure 1 shows the total amount of corporate R&D spending by the 2,500 top companies in the world and which industries and economic sectors spent the most. As illustrated, health industries (including life sciences and health-related biotechnology) spent more than \$247 billion in corporate R&D in 2021. This was just behind the category of ICT producers but ahead of ICT services and automobiles and other transport—the other largest spenders.

Figure 1: Top Industrial Sectors, Total R&D Expenditure, in Billions of U.S. Dollars²²



22. Deloitte (2019). "2019 Global life sciences outlook focus and transform accelerating change in life sciences," p. 5.

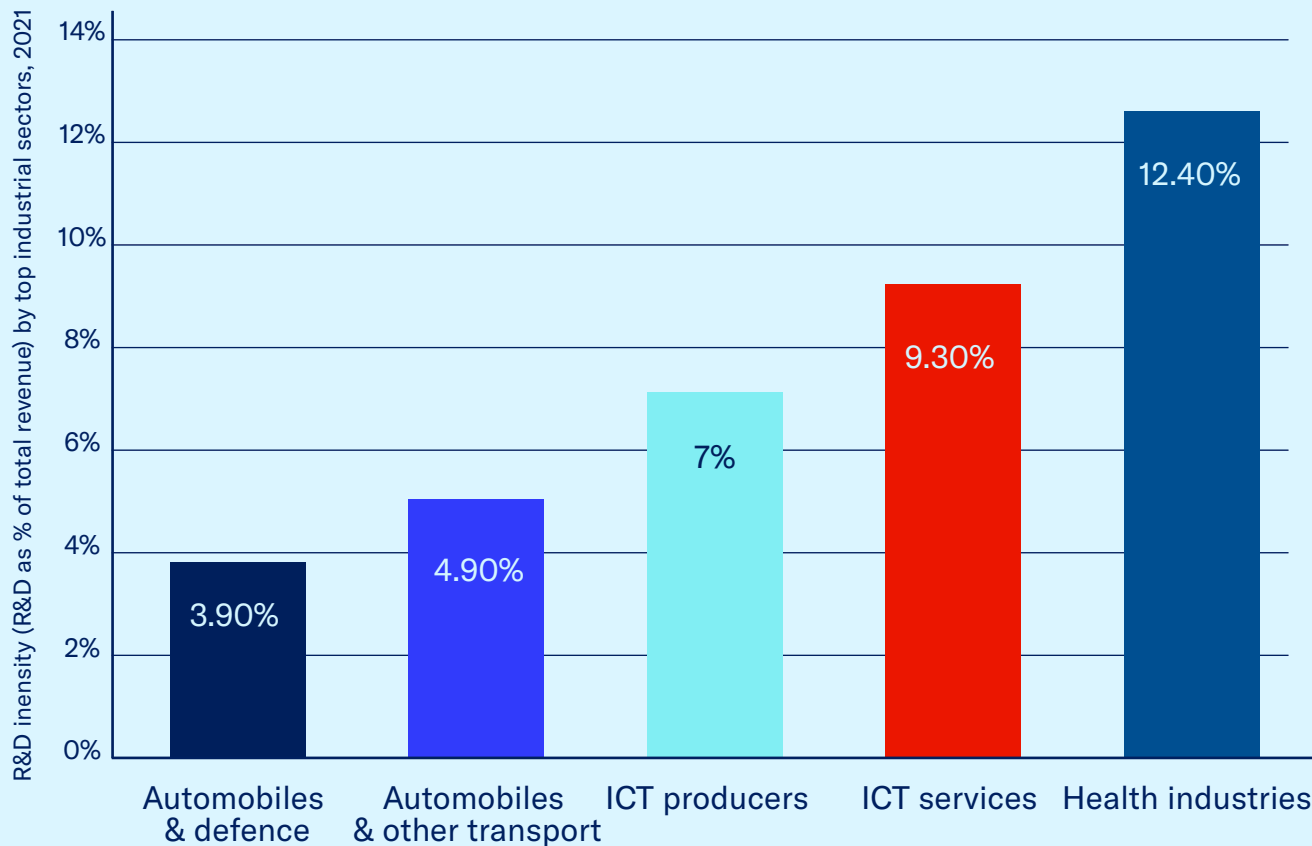
23. PhRMA (2020). "2020 PhRMA Annual Membership Survey," Washington, DC.

22. European Commission (2022). "The 2022 EU Industrial R&D Investment Scoreboard," p. 15. Euro converted to U.S. dollars using current exchange rates. The Scoreboard measures R&D expenditure by the top 2,500 companies in the world.

Similarly, looking at R&D intensity, that is, the percentage of sales invested in research, the health and life sciences sector stands out.

As Figure 2 illustrates, R&D intensity in health industries is substantially higher than all other industries, including ICT producers and ICT services.

Figure 2: Top Industrial Sectors, R&D Intensity, Select Industries²⁵



What drives this R&D investment? In short: innovation. Developing new medicines is a long-term, high-risk, resource-intensive process. The fixed costs in terms of laboratory, research facilities, and researchers are high. Compared to many other high-tech industries, developing the next groundbreaking treatment for cancer or Alzheimer’s disease requires more than just a laptop and a great idea.

As medicines become more targeted and technically sophisticated, the cost of development rises dramatically. In 1979, the total cost of developing and approving a new drug stood at \$138 million. Almost 25 years later, in 2003, this figure was estimated at \$802 million.²⁶ A 2012 estimate points to the total cost of drug development as approximately \$1.5 billion.²⁷ Tufts University research from 2016 suggests that it costs \$2.6 billion, on average, to develop a new

25. Ibid.

26. JA DiMasi et al. (2003). “The Price Of Innovation: New Estimates Of Drug Development Costs.” *Journal of Health Economics*, 22.2 (2003): 151–185.

27. D. Mestre-Ferrandiz et al. (2012). “The R&D cost of a new medicine.” London: Office of Health Economics, p. v.

drug.²⁸ On average, only one to two of every 10,000 synthesized, examined, and screened compounds in basic research will

successfully pass through all stages of R&D and go on to become a marketable drug.

The Importance of Clinical Research Within Life Sciences R&D

Clinical trials are fundamental components of this life sciences research and development process. As mentioned, the main purpose of clinical trials is to test and provide proof of the safety, quality, and efficacy of new medicines or new uses, forms, or dosages of existing medicines. Clinical trials are conducted within a highly controlled and studied environment where all aspects of a drug candidate are monitored, recorded, and subject to high levels of scrutiny and evaluation. The clinical research process includes complying with a wide range of regulations governing international best practices related to the quality, safety, and efficacy of medicines. This includes, for instance, Good Laboratory Practice guidelines on conducting toxicity studies, Good Manufacturing Practice, and protecting the rights of patients through Good Clinical Practice. Clinical research does not stop. In this sense, life sciences innovation is iterative with clinical trials, and product development is an ongoing process.

Without clinical trials, it would be exceedingly difficult to test the safety, quality, and efficacy of a proposed new medical technology. As mentioned, life sciences research is inherently a high-risk and costly endeavor with relatively low prospects of R&D success. More than 90% of clinical drug development ends in failure.²⁹ And the cost of developing new medicines remains high at an estimated \$2 billion.³⁰ Most of the expenditure and risk in conducting clinical trials are borne by the private sector. For example, in its 2023 “The Research and Development Pipeline: A Primer,” Research America found that in the United States, the life sciences industry accounted for approximately 70% of all U.S. investment in life sciences R&D; the federal government—largely through the National Institutes of Health—accounted for around 20%.³¹ In this sense, although the nature of clinical research has changed over the past few decades with new development technologies emerging, clinical research is still a fundamental cornerstone of modern life sciences and medical development. Figures 3 and 4 provide an overview of the drug development process and where in that process clinical trials take place.

28. JA DiMasi, HG Grabowski, & RW Hansen (2016). “Innovation in the biopharmaceutical industry: New estimates of R&D costs,” *Journal of Health Economics*, Vol. 47, May 2016, 20–33.

29. Sun D, Gao W, Hu H, Zhou S (2022). “Why 90% of clinical drug development fails and how to improve it?” *Acta Pharm Sin B*. 2022 Jul; 12(7): 3049–3062.

30. Hinkson IV, Madej B, Stahlberg EA (2020). Accelerating therapeutics for opportunities in medicine: a paradigm shift in drug discovery. *Front Pharmacol*. 2020;11:770.

31. Research America (2023). “The Research and Development Pipeline: A Primer,” 1–2.



Figure 3: The Life Sciences R&D Process

Research and discovery:

Scientists attempt to isolate new chemical or biological entities using advanced screening and synthesizing techniques.

Preclinical development:

Initial safety tests and assessment studies, such as toxicology, are performed on animals.

Clinical development:

Phase I:

The initial phase tests a drug candidate in 20 to 100 healthy volunteers to assess how the body processes it and what adverse effects arise. A drug must show a minimum level of safety to move to the next phase of studies.

Phase II:

This phase examines a drug candidate's effectiveness in treating a targeted disease relative to other existing medicines or to a placebo. It explores whether the candidate acts against the disease, if it causes any adverse reactions in patients, and how this measures up to existing treatments. Studies involve 100 to 500 volunteers, all of whom have the targeted disease or condition.

Phase III:

If the candidate is proven safe and effective in the first two phases, the study is shifted to a larger scale, from 1,000 to 5,000 subjects. Studies test the safety and effectiveness of the drug candidate in different populations and conditions. This phase generates extensive data on the candidate to understand as clearly as possible the safety risks associated with the drug and to identify the right dosage and mode of use. Because of the scale of operations, Phase III studies are the most costly and time-consuming trials.

Registration:

Results of preclinical and clinical studies and proof of meeting international standards are submitted to drug regulatory authorities for their review.

Post-marketing study:

Biopharmaceutical companies must submit a plan for ongoing monitoring and study of the drug as part of its approval for marketing. These studies are intended to safeguard larger-scale use of the drug by monitoring any adverse effects that become evident and identifying what appears to be the most appropriate and effective manner of use. Postmarketing studies typically provide the largest amount of evidence on a drug relative to data gathered in earlier phases.

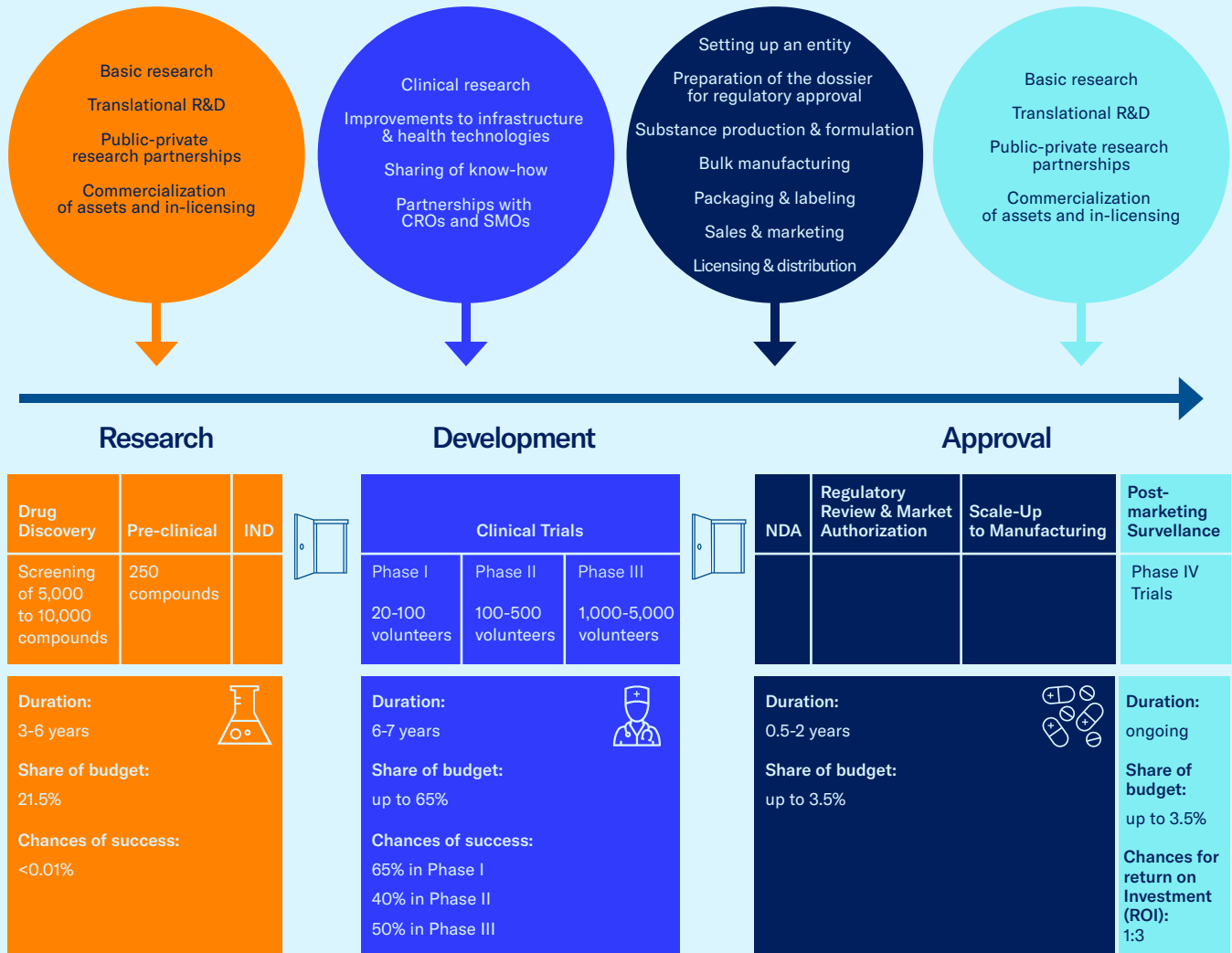
Source: Pugatch Consilium, based on Food and Drug Administration (2014).³²

32. U.S. Food and Drug Administration (FDA). "The FDA's Drug Review Process: Ensuring Medicines are Safe and Effective," <http://www.fda.gov/medicines/resourcesforyou/consumers/ucm143534.htm>.

The testing of drug candidates in human volunteers via clinical trials before market authorization,³³ which is divided into three main phases, represents an undertaking of six to seven years per drug candidate or between 55% and 75% of the total R&D process.³⁴ Phase II trials represent one of

the riskiest segments of the R&D process, involving a substantial investment with 100 to 500 volunteers per trial but only a 40% success rate. Figure 4 shows the time and investment typically required for each stage of the clinical research process.

Figure 4: Life Sciences R&D Process and Timeline



Source: Pugatch Consilium; adapted from PhRMA³⁵ and Nature.³⁶

A concrete example of the difficulties in developing new medicines and treatments

33. The World Health Organization defines clinical trials as “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.” See WHO, “Health topics: Clinical trials,” http://www.who.int/topics/clinical_trials/en/.

34. J Mestre-Ferrandiz et al. (2012). The R&D Cost of a New Medicine, Office of Health Economics, p. 24.

35. Pharmaceutical Research and Manufacturers of America. (2013). “2013 Biopharmaceutical Research Industry Profile,” Washington, DC: PhRMA.

36. SM Paul et al. (2010). “How to Improve R&D Productivity: The Pharmaceutical Industry’s Grand Challenge,” Nature Reviews Drug Discovery, Vol. 9, 203–214, http://www.nature.com/nrd/journal/v9/n3/fig_tab/nrd3078_F2.html.

can be seen with respect to Alzheimer’s disease. Alzheimer’s and neurodegenerative diseases are a growing challenge for the patients and families faced with the diseases and for the health system charged with caring for those affected. The Global Burden of Disease health metrics project estimates that Alzheimer’s disease and other dementias cause close to 3.5% of global deaths and an estimated 0.97% of total disability-adjusted life years.³⁷ These global figures are compounded when looking at high-income developed regions with aging populations, including Western Europe, North America, and Asia Pacific. Looking only at these high-income economies, the figures are significantly higher. In these countries, Alzheimer’s disease and other dementias account for almost 10% of deaths and 3.26% of total disability-adjusted life years. This is likely to continue to increase as the populations of many high-income economies age and economic dependency ratios increase. Yet despite this growing disease burden, the available treatment options for Alzheimer’s disease and other dementias have until recently been limited. Despite significant R&D investment over

the past two-plus decades, the availability of products that mitigate the effects of Alzheimer’s disease is extremely limited.³⁸ Given these challenges, increasing numbers of research-based manufacturers are pulling out of this therapeutic space, and relatively few companies (big or small) are investing resources in developing neurological treatments. The significant research challenge that Alzheimer’s disease poses is reflected by both the low number of new technologies under investigation and new products introduced into the marketplace. Between 1998 and 2015, 104 drugs were estimated to be under development for treating Alzheimer’s disease.³⁹ Only three of these drugs were subsequently approved into actual commercial products. Only in the past few years have new products, such as Leqembi, Aduhelm, and Donanemab, been approved for market or have shown significant positive results in late-phase clinical trials and have changed the treatment landscape for patients with Alzheimer’s disease.

More Than R&D: The Broader Social Value of Conducting Clinical Trials

In addition to their centrality to the life sciences R&D process, clinical trials have numerous socioeconomic benefits.

Clinical trials provide patients with early access to innovative medicines, which may

literally revolutionize existing treatments. In fact, clinical trials enable advance access to treatments that may continue beyond the duration of the clinical trial. In this sense, the availability of a trial can be the difference between a patient gaining access to a given

37. Institute for Health Metrics and Evaluation (2016). “GBD Compare,” data visualization.

38. One estimate suggests that the failure rate for Alzheimer’s disease drugs in Phases II and III of clinical testing has been virtually 100% (99.6%). See R. Wright (2016) “Convince Me Why Investing in Alzheimer’s R&D Is a Good Idea,” Life Science Leader, May 1, 2016.

39. PhRMA (2012). Researching Alzheimer’s Medicines: Setbacks and Stepping Stones, 12–13.

novel treatment in research and waiting for several years until the product has been fully developed and globally launched. For patients with rare and/or difficult and terminal diseases, the availability of local trials can be a matter of life or death.

Clinical trials also help local physicians participate in cutting-edge research and become members of multicenter research networks. Such experience helps build R&D expertise, experience, and prestige, and it expands the ability of local researchers to publish their research and to become key opinion leaders in their field. This often leads to improvements to infrastructure—hospitals, clinics, and health technologies—in local communities. Participation in multinational, cutting-edge research helps ensure that clinical trials and sites meet international standards of good clinical practice and exposes clinicians to new research techniques and treatment strategies. In this sense, the growth and conduct of clinical trials improve the overall medical research infrastructure and experience in an economy and/or region. A tangible and recent illustration is the immense clinical research effort in the United States to develop new medicines, vaccines, and therapies to be used against COVID-19. According to the U.S. Chamber of Commerce, almost 2,000 clinical trials were conducted in all 50 states, including 97% of congressional districts.⁴⁰

Finally, representing the largest portion of life sciences R&D spending, clinical research can have significant positive direct and indirect macroeconomic benefits both nationally and regionally in the economy in which it takes place. As detailed earlier, the research-based life sciences industry is one of the most research-intensive industries in the world, investing billions of dollars a year in R&D and innovation, most of which is spent on clinical trials.

40. U.S. Chamber of Commerce GIPC (2023). "Discover & Deliver: All-of-Nation Effort to Find Safe and Effective Solutions to Eradicate the Global Pandemic," July 21, 2020.

Trends in Clinical Trial Activity: Comparing the United States with a Sample of Major OECD Economies

Having described the life sciences R&D process and the importance of clinical trials to the development of new medicines and health technologies, this section presents an analysis of key trends in international clinical trial activity. Specifically, it compares the experience of the United States with nine major OECD economies: Australia, Canada, France, Germany, Italy, Japan, South Korea, Spain, and the United Kingdom. As mentioned, despite having many of the same scientific and technological strengths as the United States, these economies have

consistently lagged rates of clinical research and life sciences innovation in the United States. Significantly, as the data here show, this disparity only grows when examining more complex areas of clinical research. As the experience of these economies strongly suggests, the imposition of national price controls and cost-containment measures on the life sciences sector undermines many of the key incentives to invest and innovate in life sciences R&D.

Clinical Trials Data Sources

Clinical trial registries exist at national, regional, and international levels. At the national and regional levels, registries differ significantly in registry criteria, adherence to quality standards, and data availability, which can lead to discrepancies

in the number of clinical trials registered. International-level registries conform with the highest standards of quality, validity, and transparency and are therefore preferred by clinical trial researchers and sponsors.

Two major international registries exist:

- The World Health Organization’s International Clinical Trials Registry Platform (ICTRP)
- The U.S. National Institutes of Health’s clinicaltrials.gov

(In addition to the ICTRP and clinicaltrials.gov, there is the regional EU Clinical Trial Register. This register contains a relatively small number of registered trials, under 65,000 trials, up to and including 2022. The register is being decommissioned and transitioned into a new clinical trials information system portal with trials from 2023.)

Like all databases, neither the ICRP nor clinicaltrials.gov is perfect. This report uses clinicaltrials.gov as the source for clinical trials data for the following reasons.

To begin, the World Health Organization’s ICTRP does not maintain a registry of its own. Rather, it provides a publicly available platform for accessing clinical trial data across all World Health Organization–member states based on data retrieved from national and regional registries. However, the

responsibility for the registration data lies with the national and regional entities, many of which do not meet the required standards. And although the ICTRP contains a comparable number of trials to clinicaltrials.gov, it has more limited quality control and searchability compared to clinicaltrials.gov. In contrast, clinicaltrials.gov includes quality control and standardization over its data. It is also mandatory to register a drug or medical device candidate designated for Food and Drug Administration (“FDA”) approval per federal regulations. Finally, clinicaltrials.gov is broadly recognized in the research literature as the most reliable and encompassing registry. For example, the challenge of quality control and searchability with the ICTRP’s registry was highlighted by a 2017 article in the *Journal of Clinical Epidemiology*.⁴¹ Similarly, a more recent (2022) study by Charles River and Associates for the European Federation of Pharmaceutical Industries and Associations comparing levels of clinical research between Europe and other regions around the world compared the relative merits of both the ICTRP and clinicaltrials.gov. It chose clinicaltrials.gov as the best source.⁴²

Types of Clinical Research Examined

Clinical trial registries provide a picture of the number, type, and phase of clinical trials in an economy individually and in international comparison.

The registration of a clinical trial in a clinical trial registry is as follows:

1. A scientific and ethical requirement under the Declaration of Helsinki

41. Knelangen, M. et al. (2017). “Trial registry searches for randomized controlled trials of new drugs required registry-specific adaptation to achieve adequate sensitivity,” *Journal of Clinical Epidemiology*, Vol. 94, 69–75.

42. Charles River and Associates for the European Federation of Pharmaceutical Industries and Associations (EFPIA) (2022). *Factors affecting the location of biopharmaceutical investments and implications for European policy priorities*, 10–15.

2. A requirement for publication by the International Committee of Medical Journal Editors
3. A legal requirement in most economies

A clinical trial registry includes the trial's start and finish date, phase, medical condition(s) studied, intervention(s), location(s), sponsors, and general subjects' data. This enables a broad analysis of the various types of clinical trial activity taking place in an economy and around the world. Examining clinical trials data reveals key attributes of an economy's life sciences R&D environment, including research capacity and performance. Key performance measures analyzed in this report include the following:

- **Overall clinical trial activity:**
A high absolute number of trials suggests an economy is an attractive host for life sciences R&D and has achieved economies of scale in life sciences R&D.
- **R&D capacity:**
The types of trials taking place and disease areas suggest the technical R&D capacity in an economy. For example, trials in complex therapeutic areas such as oncology, Alzheimer's disease, diabetes, obesity, and cardiovascular diseases require a higher level of R&D capacity than more basic bioequivalence studies related to generic follow-on products.

- **Innovativeness:**
In what types of phases are clinical trials in an economy concentrated? Early-phase research (phases I and II) suggests cutting-edge, innovative research is taking place. Early-phase trials represent initial human testing of a drug candidate's safety and efficacy and therefore typically require controlled environments and high-quality human resources and infrastructure.
- **Biotechnology capacity:**
How many trials focus on biologics as opposed to chemical entities? Biologic and biotechnology-based medicines and technologies are increasingly used in the treatment of some of the most difficult medical conditions today and in new research techniques. For example, most vaccines and therapeutics developed against COVID-19 are based on new, complex, biotechnology-based research. Given the size, complexity, and inherent instability of a biologic molecule, the testing of a biologic drug candidate's safety and efficacy within a clinical trial necessitates a highly controlled environment in which transportation and storage of the drug are controlled, the trial protocols are strictly adhered to, and patients are monitored carefully.

Table 1 shows the specific categories and types of clinical trials data that this report retrieved for the United States and the nine OECD comparator economies registered in clinicaltrials.gov to date.

Table 1: Clinical Trials Data Retrieved

- The number of all clinical trials
- The number of all early-phase (phase I and phase II) trials
- The number of clinical trials on biologic medicines
- The number of early-phase (phase I and phase II) clinical trials on biologic medicines
- The number of clinical trials related to cancer
- The number of early-phase (phase I and phase II) clinical trials related to cancer
- The number of clinical trials related to Alzheimer's disease
- The number of early-phase (phase I and phase II) clinical trials related to Alzheimer's disease
- The number of clinical trials related to diabetes
- The number of early-phase (phase I and phase II) clinical trials on diabetes
- The number of clinical trials related to obesity
- The number of early-phase (phase I and phase II) clinical trials related to obesity
- The number of clinical trials related to cardiovascular diseases
- The number of early-phase (phase I and phase II) clinical trials relating to cardiovascular diseases

This report also collected clinical trial data related to industry sponsorship of clinical research.

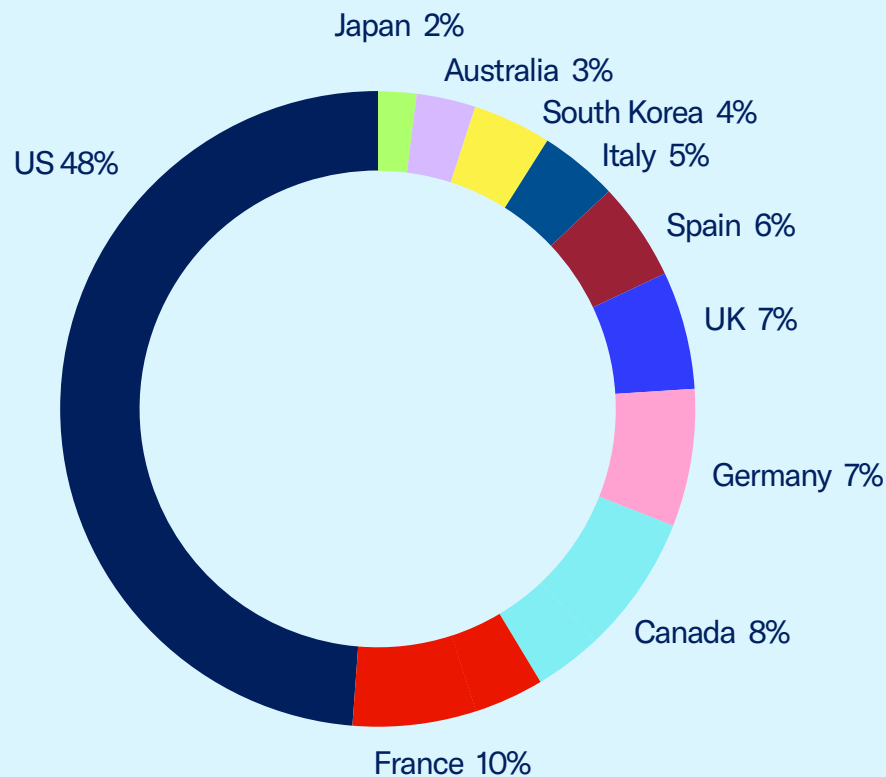
Trends in Clinical Trial Activity: Results

All Clinical Trials

Figure 5 shows the total number of clinical trials registered to date in clinicaltrials.gov for the United States and the nine

comparator economies (Australia, Canada, France, Germany, Italy, Japan, South Korea, Spain, and the United Kingdom).

Figure 5: Number of Clinical Trials Registered to Date in clinicaltrials.gov, Percentage of Combined Sample, United States and Nine Comparator Economies



As Figure 5 shows, the United States has hosted almost the same number of clinical trials as Australia, Canada, France,

Germany, Italy, Japan, South Korea, Spain, and the United Kingdom combined.

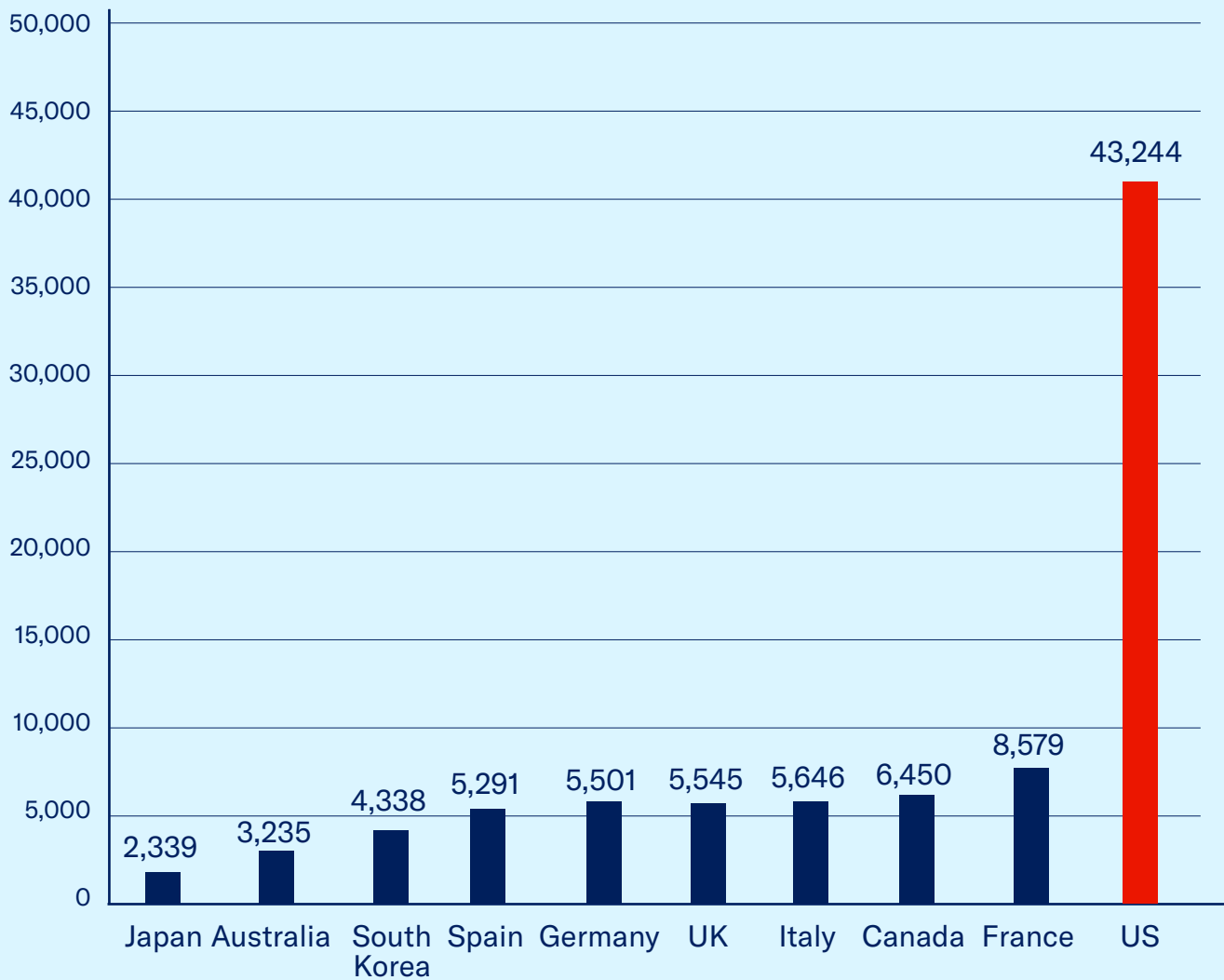
Therapeutic Subcategories: Comparing Levels of Clinical Research Related to Cancer, Alzheimer’s Disease, Diabetes, Obesity, Cardiovascular Disease, and Biologics

Figures 6 through 16 show the total number of clinical trials registered to date in clinicaltrials.gov for the United States and the nine comparator economies (Australia, Canada, France, Germany,

Italy, Japan, South Korea, Spain, and the United Kingdom) for research related to cancer, Alzheimer’s disease, diabetes, obesity, and cardiovascular disease.

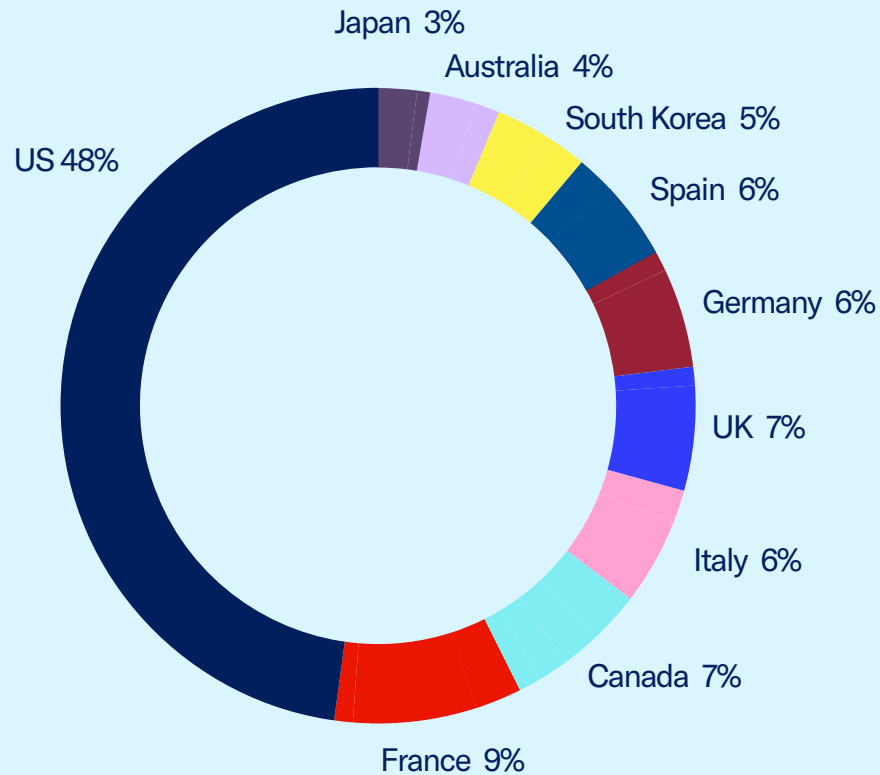
Clinical Trials Related to Cancer⁴³

Figure 6: Number of Cancer-Related Clinical Trials Registered to Date in clinicaltrials.gov, United States and Nine Comparator Economies



43. Terms and synonyms searched: cancer, neoplasm, tumor, malignancy, oncology, neoplasia, neoplastic syndrome, neoplastic disease.

Figure 7: Number of Cancer-Related Clinical Trials Registered to Date in clinicaltrials.gov, Percentage of Combined Sample, United States and Nine Comparator Economies



At the time of research, 90,168 cancer-related clinical trials were registered in clinicaltrials.gov to date in the United States and the nine comparator economies. As Figures 6 and 7 show, of these trials, the

United States was host to 43,244 trials, or 48%, and hosted almost the same number of clinical trials as Australia, Canada, France, Germany, Italy, Japan, South Korea, Spain, and the United Kingdom combined.

Clinical Trials Related to Alzheimer’s Disease

Figure 8: Number of Alzheimer’s Disease–Related Clinical Trials Registered to Date in clinicaltrials.gov, United States and Nine Comparator Economies

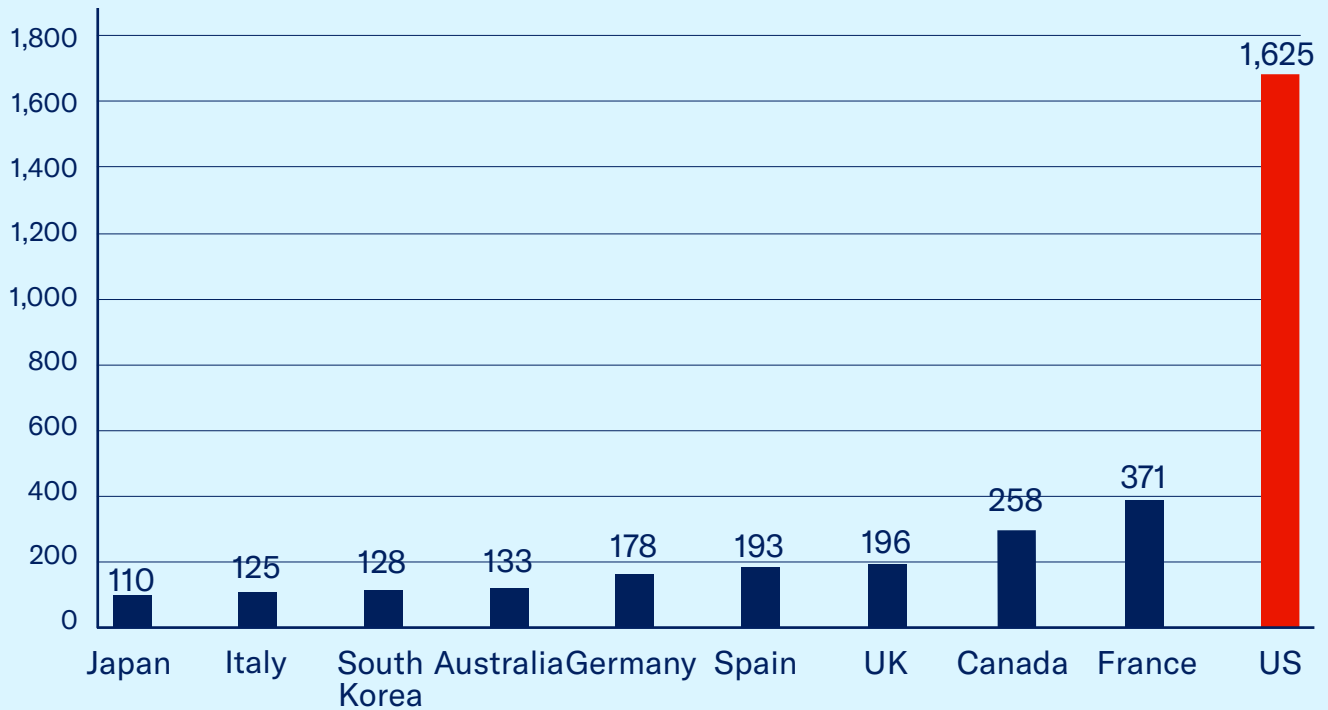
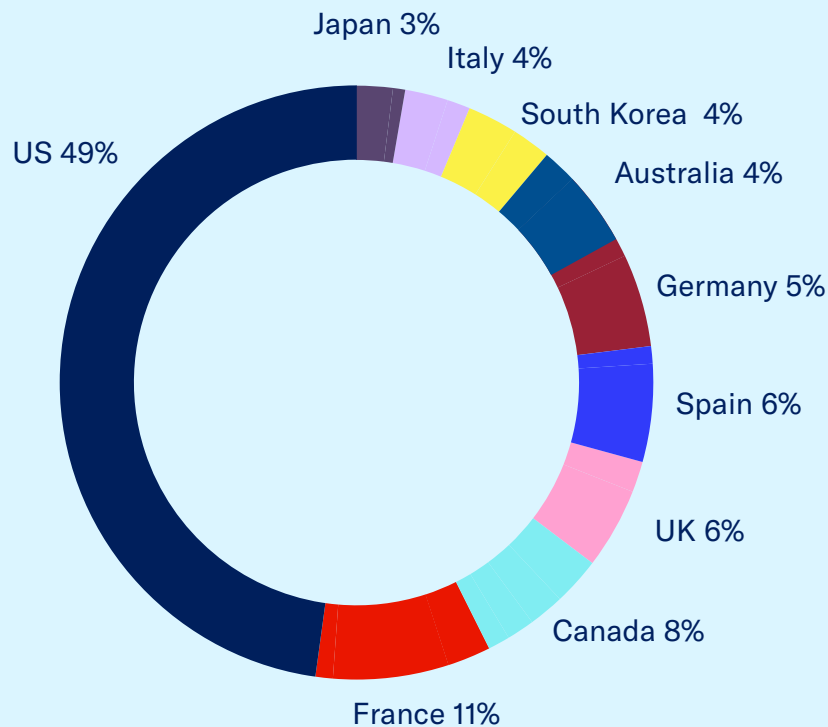


Figure 9: Number of Alzheimer’s Disease–Related Clinical Trials Registered to Date in clinicaltrials.gov, Percentage of Combined Sample, United States and Nine Comparator Economies



At the time of research, 3,317 Alzheimer’s disease–related clinical trials were registered in clinicaltrials.gov to date in the United States and the nine comparator economies. As Figures 8 and 9 show, of these trials, the

United States was host to 1,625 trials, or 49%, and hosted almost the same number of clinical trials as Australia, Canada, France, Germany, Italy, Japan, South Korea, Spain, and the United Kingdom combined.

Clinical Trials Related to Diabetes

Figure 10: Number of Diabetes–Related Clinical Trials Registered to Date in clinicaltrials.gov, United States and Nine Comparator Economies

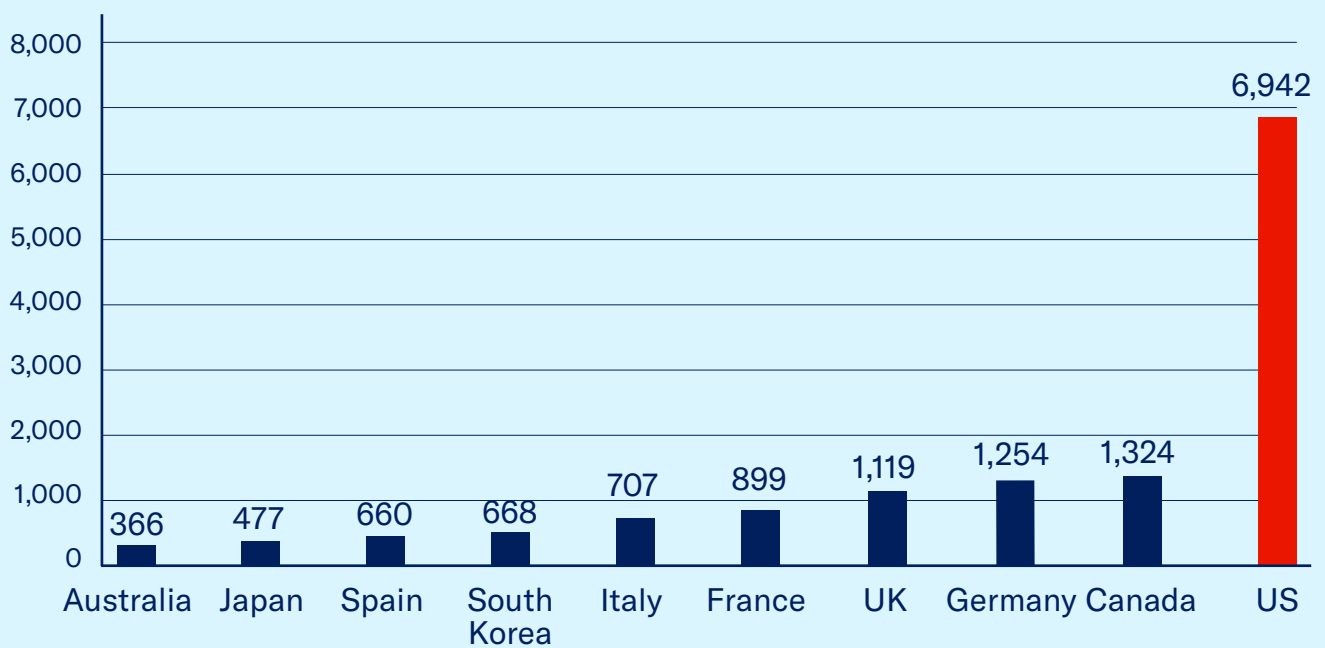
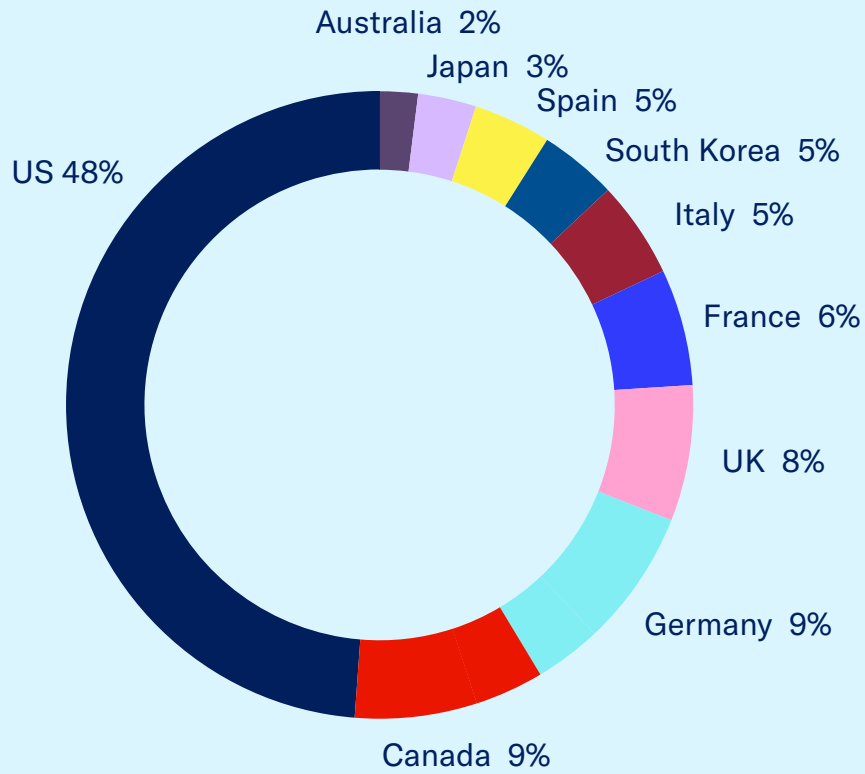


Figure 11: Number of Diabetes-Related Clinical Trials Registered to Date in clinicaltrials.gov, Percentage of Combined Sample, United States and Nine Comparator Economies



At the time of research, 14,416 diabetes-related clinical trials were registered in clinicaltrials.gov to date in the United States and the nine comparator economies. As Figures 10 and 11 show, of these trials, the

United States was host to 6,942 trials, or 48%, and hosted almost the same number of clinical trials as Australia, Canada, France, Germany, Italy, Japan, South Korea, Spain, and the United Kingdom combined.

Clinical Trials Related to Obesity

Figure 12: Number of Obesity-Related Clinical Trials Registered to Date in clinicaltrials.gov, United States and Nine Comparator Economies

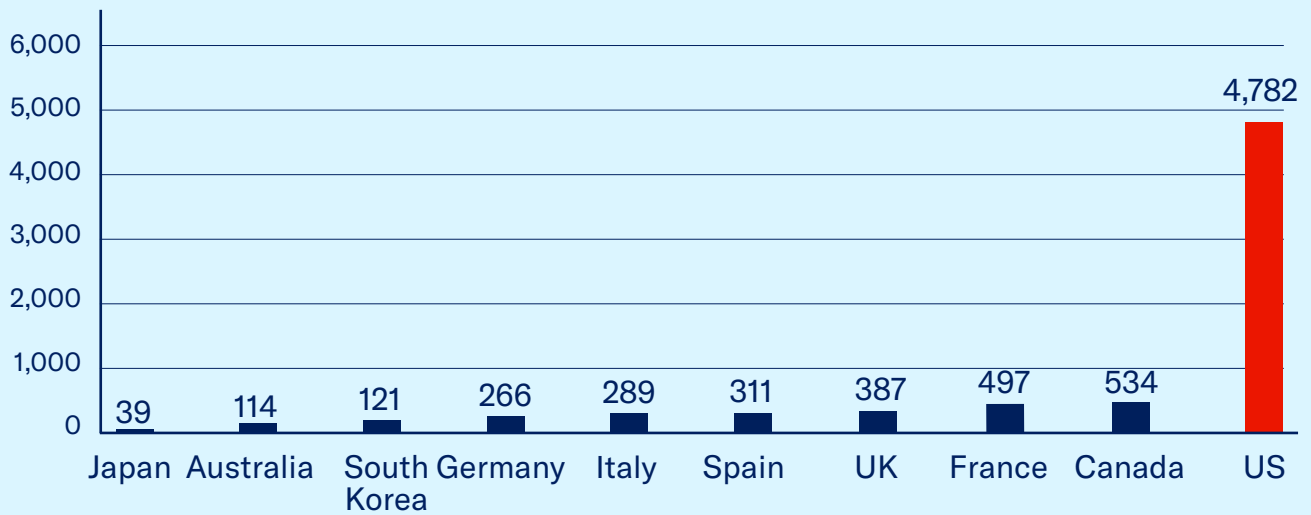
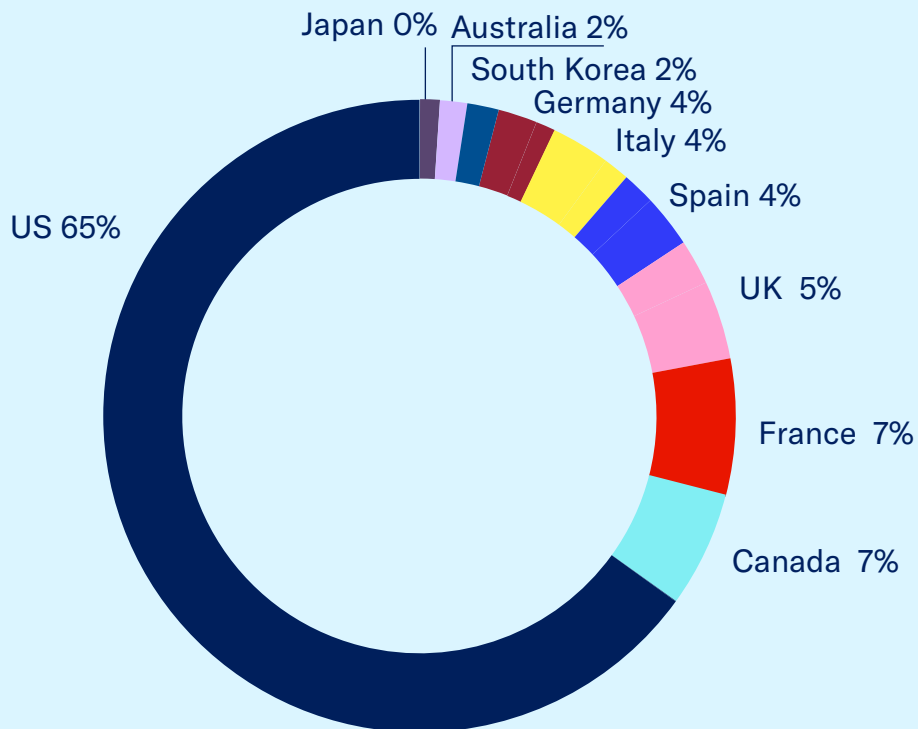


Figure 13: Number of Obesity-Related Clinical Trials Registered to Date in clinicaltrials.gov, Percentage of Combined Sample, United States and Nine Comparator Economies



At the time of research, 7,340 obesity-related clinical trials were registered in clinicaltrials.gov to date in the United States and the nine comparator economies. As Figures 12 and 13 show, of these trials, the

United States was host to 4,782, or 65%, and hosted almost double the number of clinical trials as Australia, Canada, France, Germany, Italy, Japan, South Korea, Spain, and the United Kingdom combined.

Clinical Trials Related to Cardiovascular Disease

Figure 14: Number of Cardiovascular Disease–Related Clinical Trials Registered to Date in clinicaltrials.gov, United States and Nine Comparator Economies

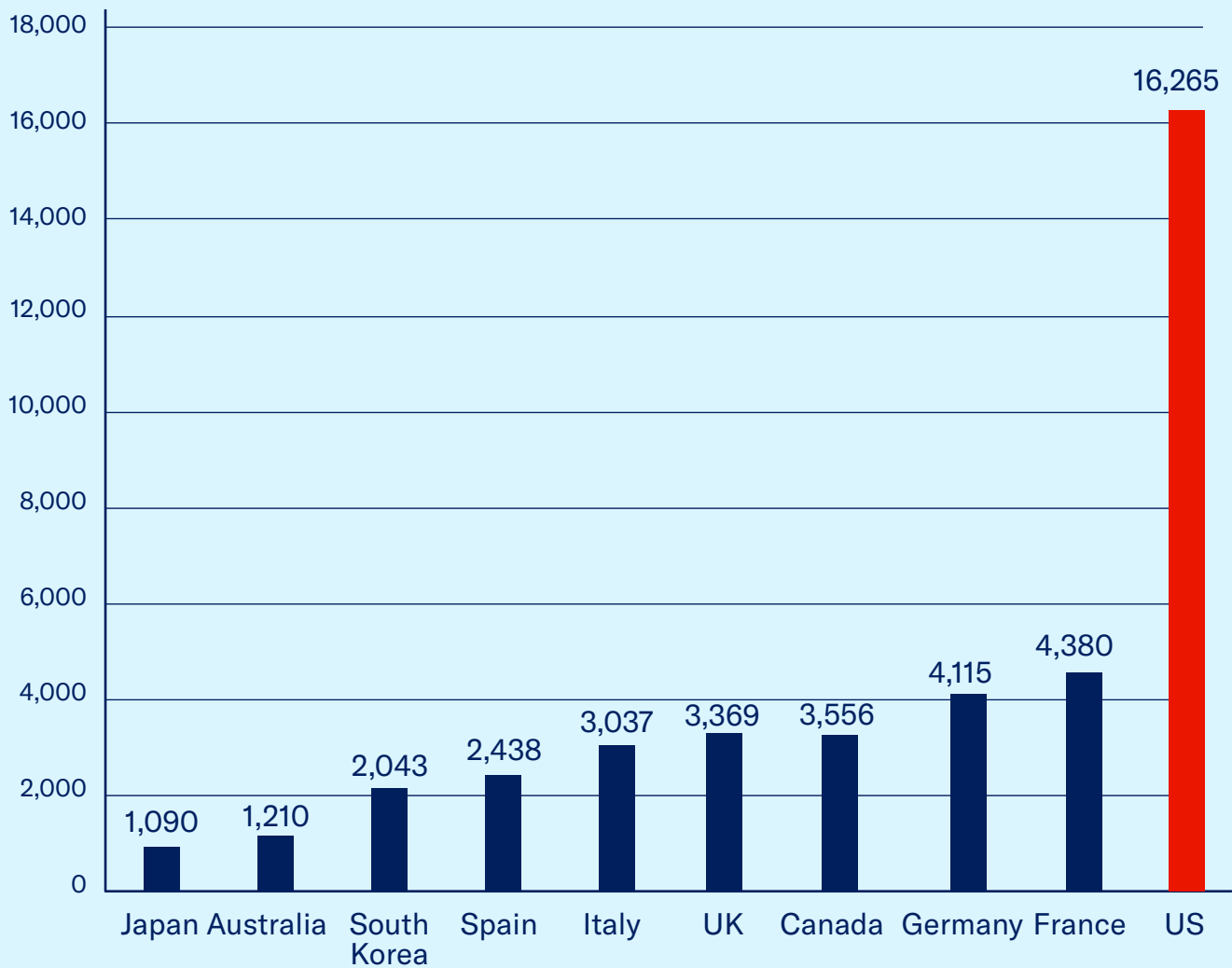
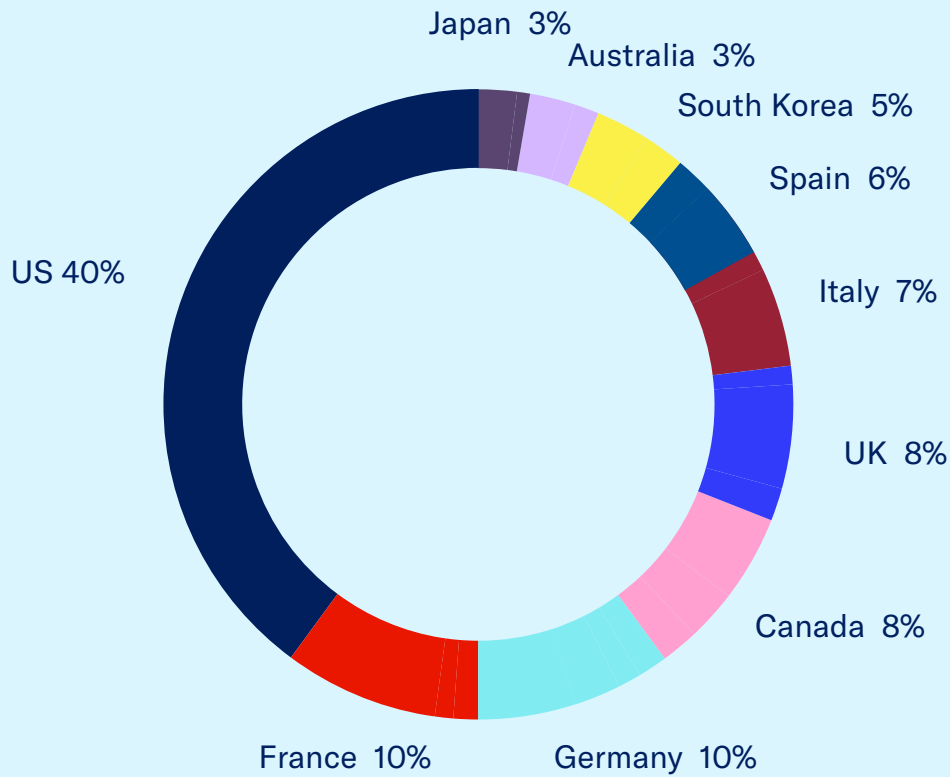


Figure 15: Number of Cardiovascular Disease–Related Clinical Trials Registered to Date in clinicaltrials.gov, Percentage of Combined Sample, United States and Nine Comparator Economies



At the time of research, 41,937 cardiovascular disease–related clinical trials were registered in clinicaltrials.gov to date in the United States and the nine comparator

economies. As Figures 14 and 15 show, of these trials, the United States was host to 16,699, or 40% of the total.

The Next Generation of Medicines: Comparing Cutting-Edge R&D and Innovation as Represented by Early-Phase Clinical Research (Phases I and II)

Figures 16 through 28 show the total number of clinical trials registered to date in clinicaltrials.gov for the United States and the nine comparator economies (Australia, Canada, France, Germany,

Italy, Japan, South Korea, Spain, and the United Kingdom) for all early-phase clinical trials and early-phase research related to cancer, Alzheimer’s disease, diabetes, obesity, and cardiovascular disease.

Early-Phase Research, All Trials

Figure 16: Number of Early-Phase Clinical Trials Registered to Date in clinicaltrials.gov, United States and Nine Comparator Economies

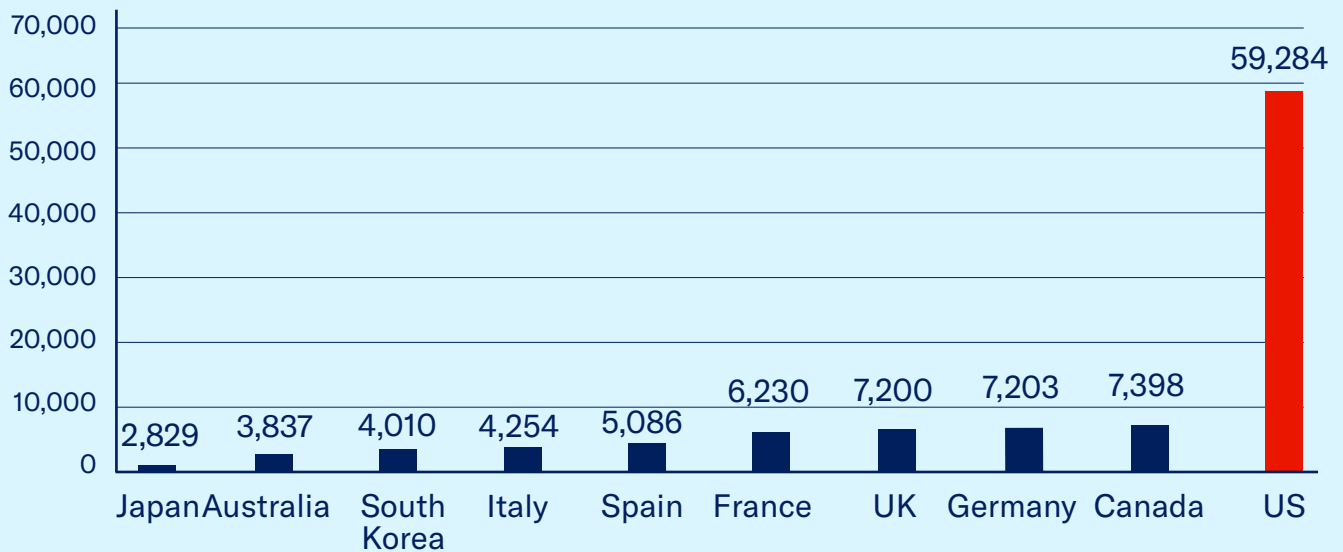
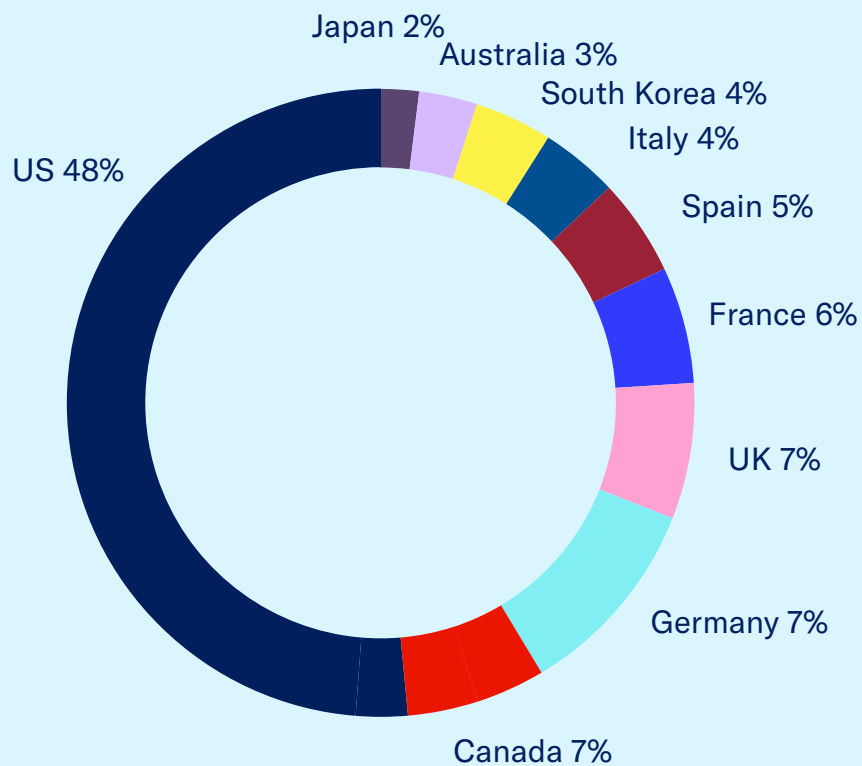


Figure 17: Number of Early-Phase Clinical Trials Registered to Date in clinicaltrials.gov, Percentage of Combined Sample, United States and Nine Comparator Economies



At the time of research, 107,331 early-phase clinical trials were registered in clinicaltrials.gov to date in the United States and the nine

comparator economies. As Figures 16 and 17 show, of these trials, the United States was host to 59,284, or 55% of the total.

Early-Phase Research, Clinical Trials Related to Cancer

Figure 18: Number of Early-Phase Clinical Trials Related to Cancer Registered to Date in clinicaltrials.gov, United States and Nine Comparator Economies

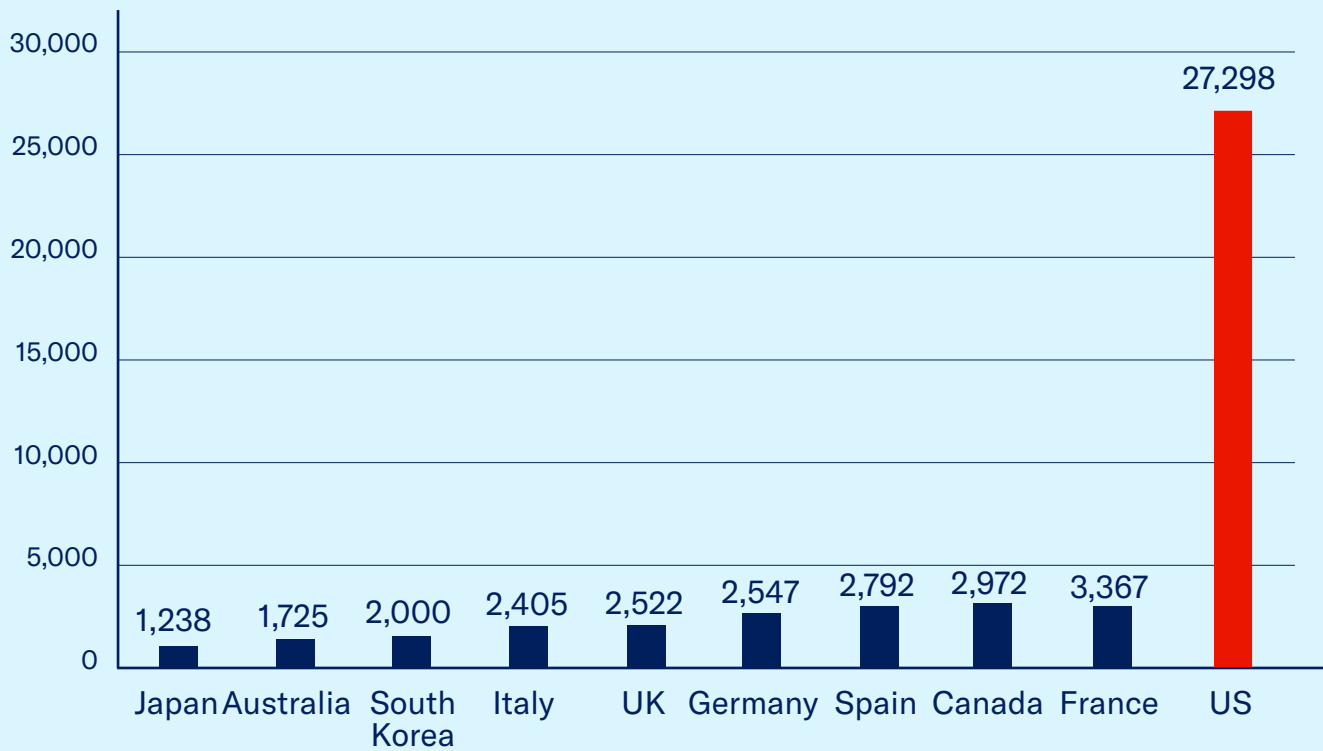
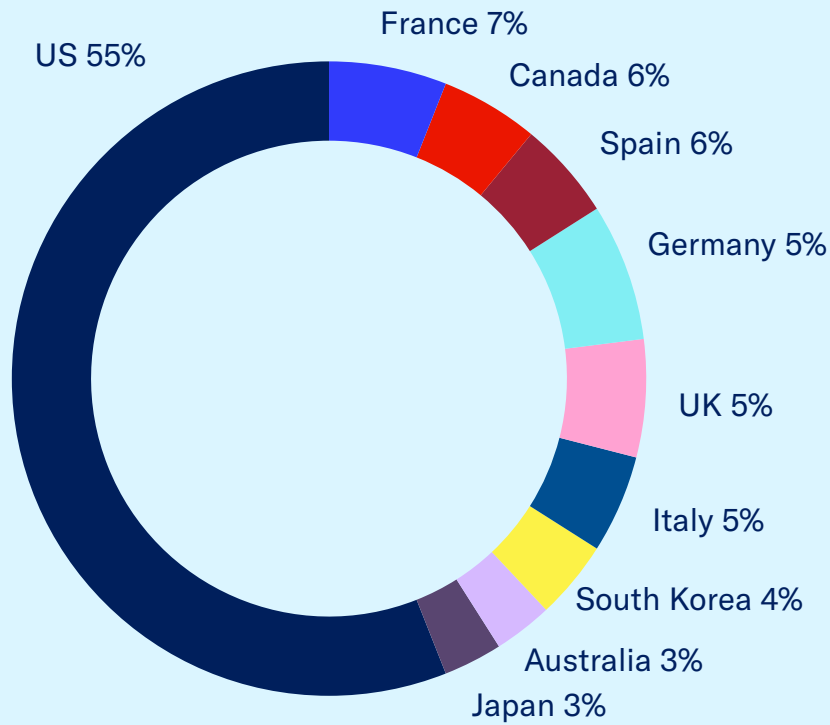


Figure 19: Number of Early-Phase Clinical Trials Related to Cancer Registered to Date in clinicaltrials.gov, Percentage of Combined Sample, United States and Nine Comparator Economies



At the time of research, 48,866 early-phase clinical trials related to cancer were registered in clinicaltrials.gov to date in the United States and the nine comparator economies. As Figures 18 and 19 show, of these trials, the United States was host to 27,298, or 56% of the total.

Early-Phase Research, Clinical Trials Related to Alzheimer’s Disease

Figure 20: Number of Early-Phase Clinical Trials Related to Alzheimer’s Disease Registered to Date in clinicaltrials.gov, United States and Nine Comparator Economies

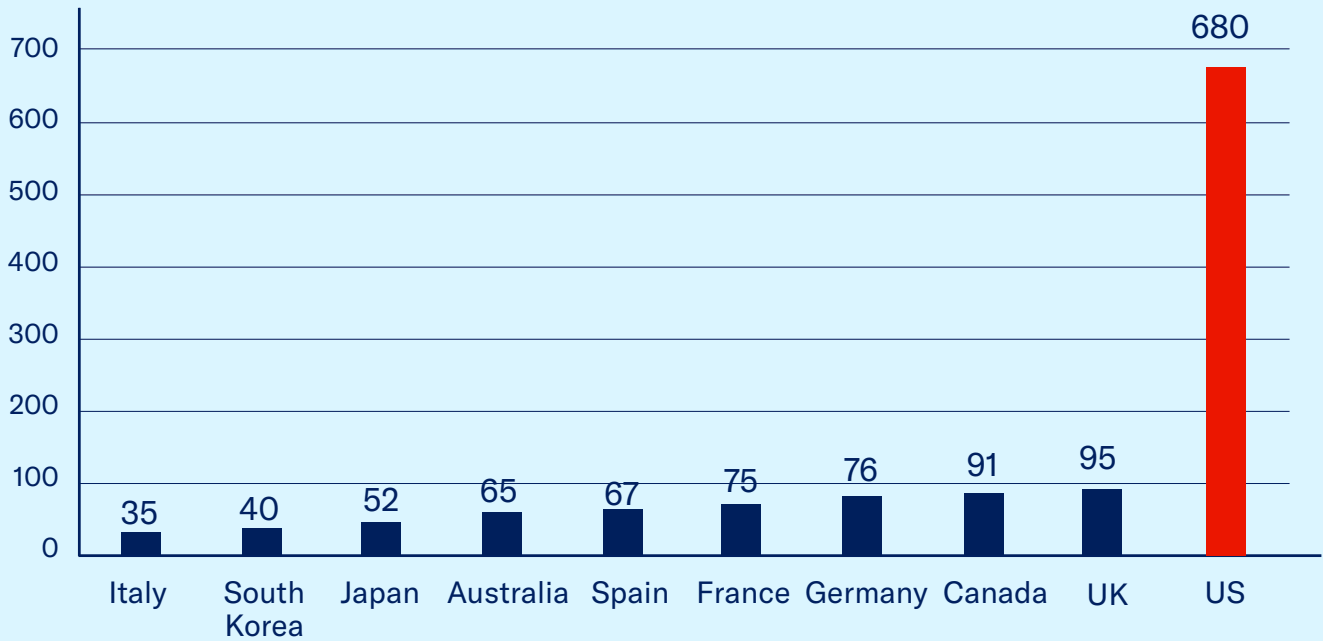
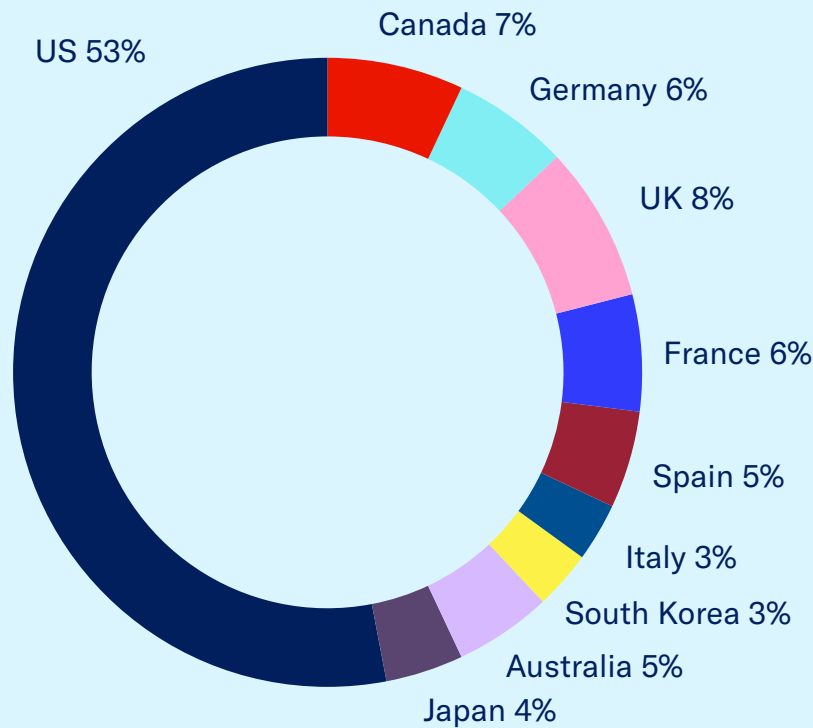


Figure 21: Number of Early-Phase Clinical Trials Related to Alzheimer’s Disease Registered to Date in clinicaltrials.gov, Percentage of Combined Sample, United States and Nine Comparator Economies



At the time of research, 1,276 early-phase clinical trials related to Alzheimer’s disease were registered in clinicaltrials.gov to date in the United States and the nine

comparator economies. As Figures 20 and 21 show, of these trials, the United States was host to 680, or 53% of the total.

Early-Phase Research, Clinical Trials Related to Diabetes

Figure 22: Number of Early-Phase Clinical Trials Related to Diabetes Registered to Date in clinicaltrials.gov, United States and Nine Comparator Economies

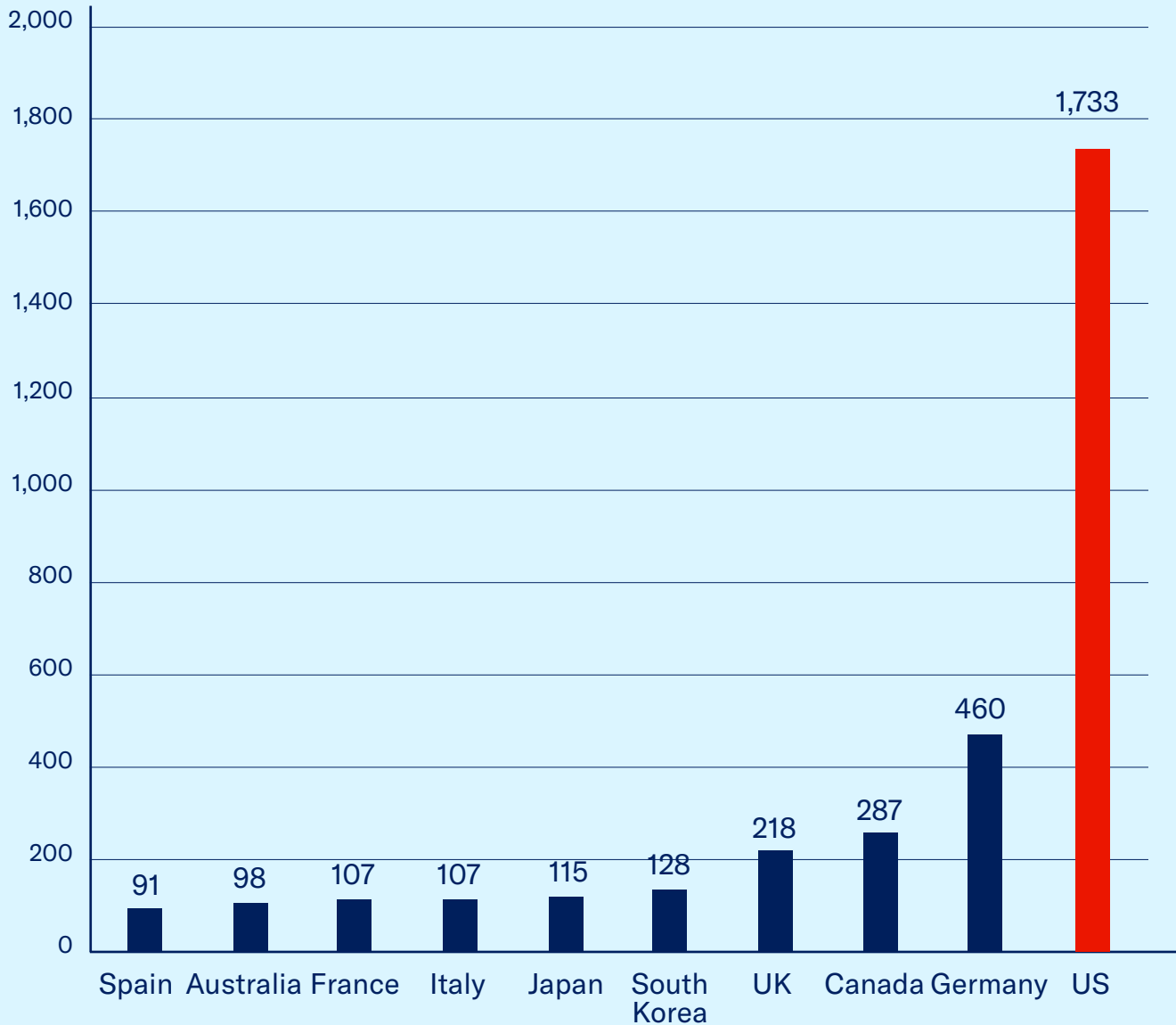
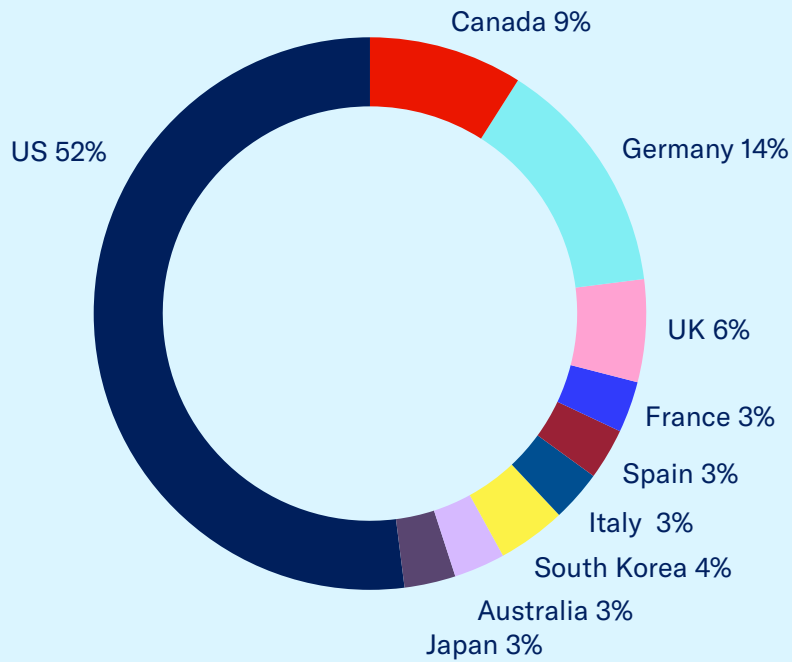


Figure 23: Number of Early-Phase Clinical Trials Related to Diabetes Registered to Date in clinicaltrials.gov, Percentage of Combined Sample, United States and Nine Comparator Economies



At the time of research, 3,344 early-phase clinical trials related to diabetes were registered in clinicaltrials.gov to date in the United States and the nine comparator economies. As Figures 22 and 23 show, of these trials, the United States was host to 1,733, or 52% of the total.

Early-Phase Research, Clinical Trials Related to Obesity

Figure 24: Number of Early-Phase Clinical Trials Related to Obesity Registered to Date in clinicaltrials.gov, United States and Nine Comparator Economies

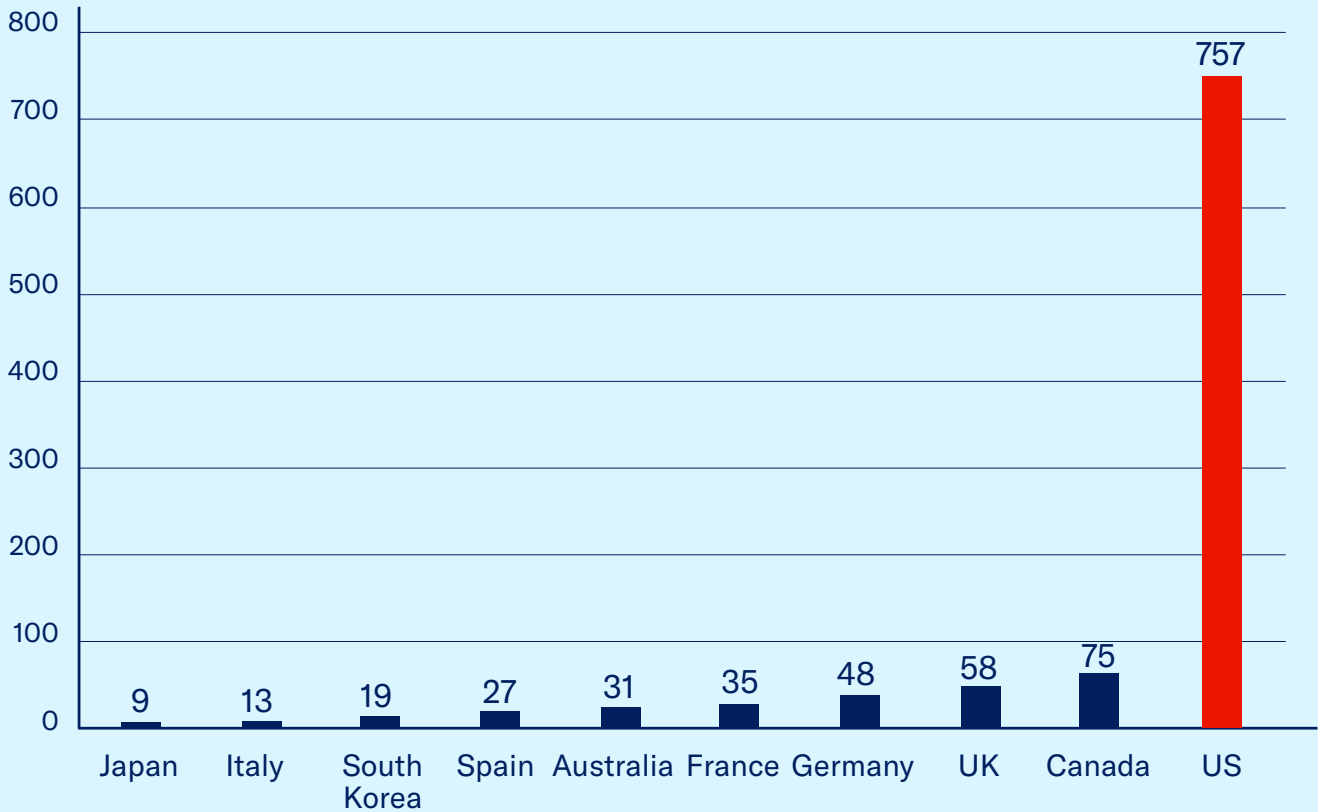
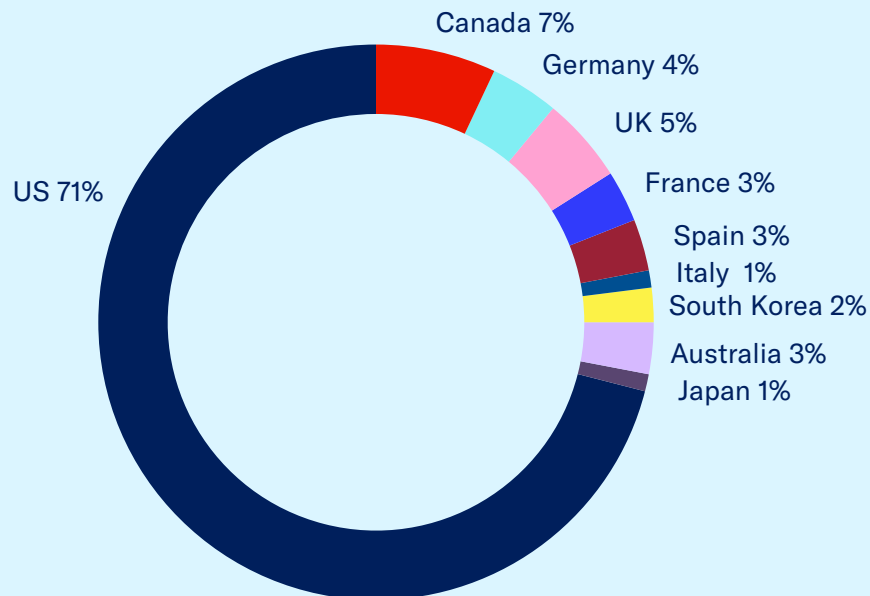


Figure 25: Number of Early-Phase Clinical Trials Related to Obesity Registered to Date in clinicaltrials.gov, Percentage of Combined Sample, United States and Nine Comparator Economies



At the time of research, 1,072 early-phase clinical trials related to obesity were registered in clinicaltrials.gov to date in the United States and the nine

comparator economies. As Figures 24 and 25 show, of these trials, the United States was host to 757, or 71% of the total.

Early-Phase Research, Clinical Trials Related to Cardiovascular Disease

Figure 26: Number of Early-Phase Clinical Trials Related to Cardiovascular Disease Registered to Date in clinicaltrials.gov, United States and Nine Comparator Economies

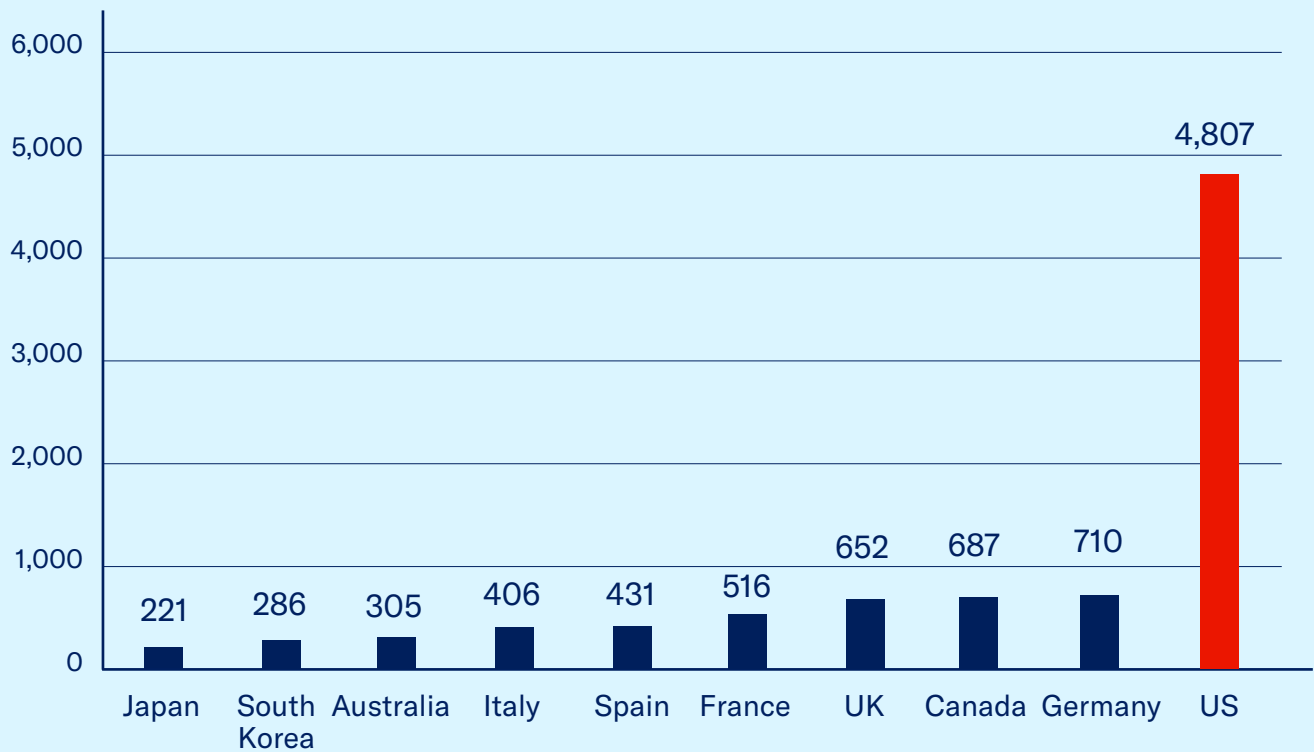
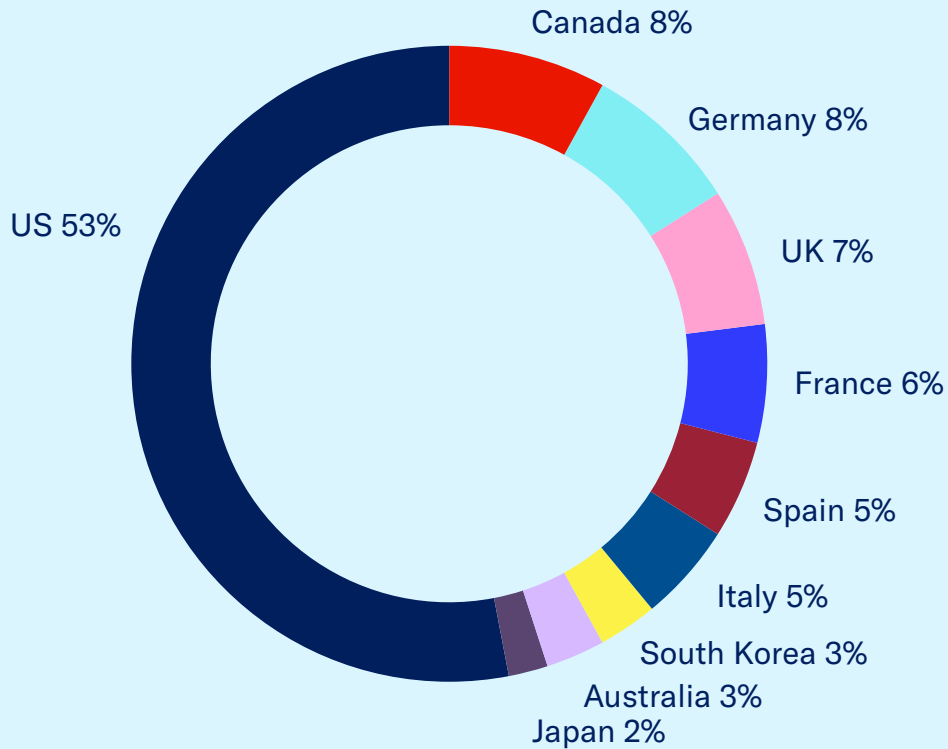


Figure 27: Number of Early-Phase Clinical Trials Related to Cardiovascular Disease Registered to Date in clinicaltrials.gov, Percentage of Combined Sample, United States and Nine Comparator Economies



At the time of research, 9,021 early-phase clinical trials related to cardiovascular disease were registered in clinicaltrials.gov to date in the United States and the nine comparator economies. As Figures 26 and 27 show, of these trials, the United States was host to 4,807, or 53% of the total.

R&D Activities Related to Biologics

How many trials focus on biologics as opposed to chemical entities? Biologic and biotechnology-based medicines and technologies are increasingly used in the treatment of some of the most difficult

medical conditions today and in new research techniques. For example, most vaccines and therapeutics developed against COVID-19 are based on new, complex, biotechnology-based research.

Figure 28: Number of Biologics-Related Clinical Trials Registered to Date in clinicaltrials.gov, United States and Nine Comparator Economies

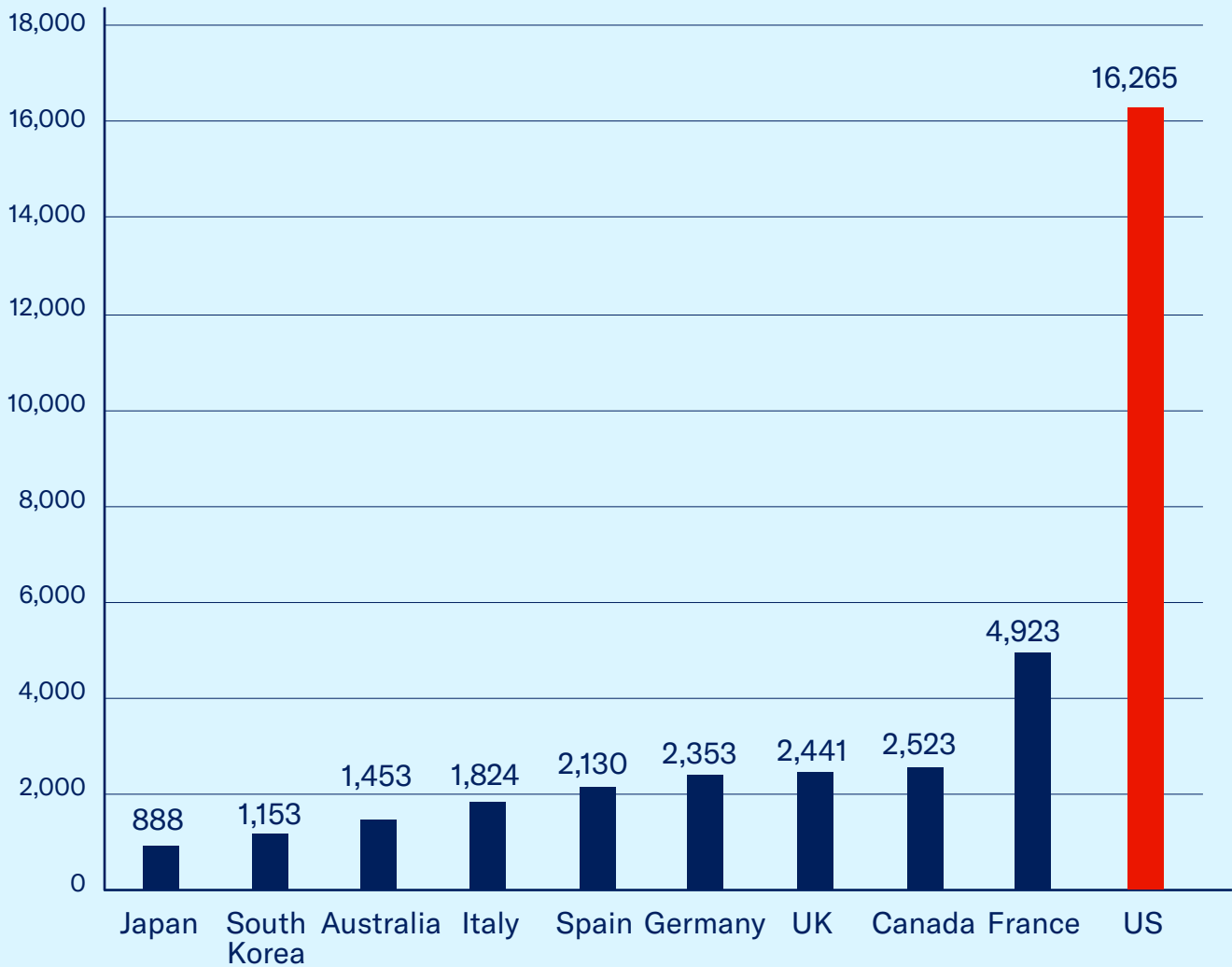
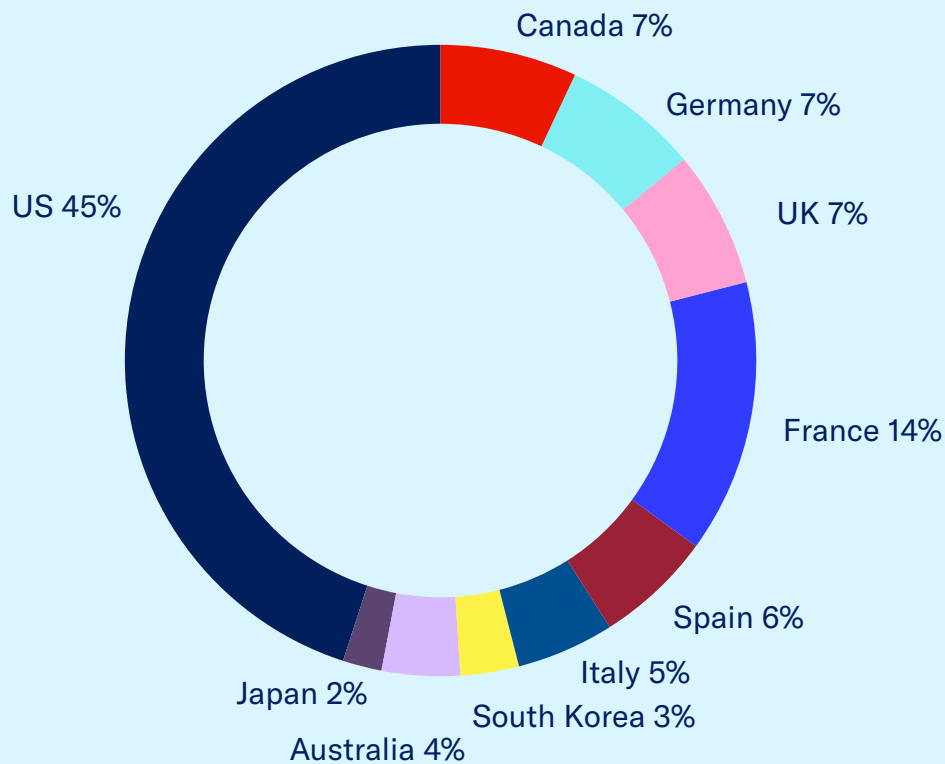


Figure 29: Number of Biologics-Related Clinical Trials Registered to Date in clinicaltrials.gov, Percentage of Combined Sample, United States and Nine Comparator Economies



At the time of research, 35,953 biologics-related clinical trials were registered in clinicaltrials.gov to date in the United States and the nine comparator

economies. As Figures 28 and 29 show, of these trials, the United States was host to 16,699, or 45% of the total.

Figure 30: Number of Early-Phase Clinical Trials Related to Biologics Registered to Date in clinicaltrials.gov, United States and Nine Comparator Economies

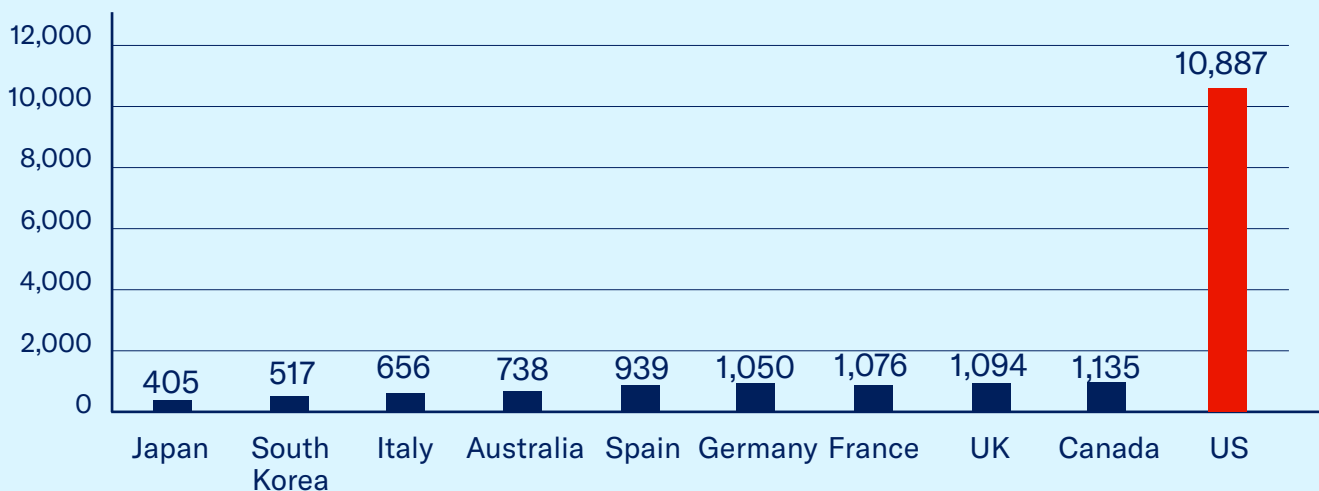
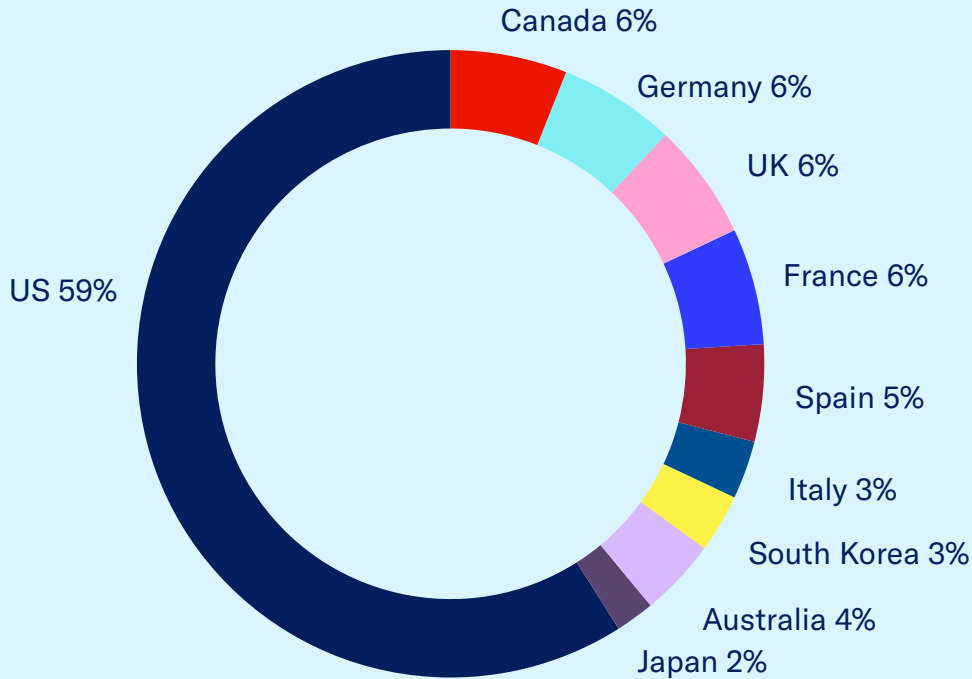


Figure 31: Number of Early-Phase Clinical Trials Related to Biologics Registered to Date in clinicaltrials.gov, Percentage of Combined Sample, United States and Nine Comparator Economies



At the time of research, 18,497 early-phase clinical trials related to cardiovascular disease were registered in clinicaltrials.gov to date in the United States and the nine

comparator economies. As Figures 30 and 31 show, of these trials, the United States was host to 10,887, or 59% of the total.

R&D Activities Related to Pain Management

The IRA is likely to negatively affect research on pain management. Research released in 2023 by the Biotechnology Innovation Organization showed a dearth of new medical innovation and investment in pain management. The study found that current levels of venture capital investment and clinical research pipelines were small and decreasing. In 2021, the amount of venture capital raised for research in pain and addiction was \$228 million; this compares to almost \$10 billion raised for venture capital investment in cancer research.⁴⁴ The study found that the level of

clinical research in pain therapeutics had declined by 44% over the past five years from 220 active programs to 124 today. The study also found that the success rate in developing new medicines and gaining FDA approval was significantly lower for pain medicines than for other disease areas. With respect to the IRA, the study concluded “that the newly enacted Inflation Reduction Act may create downward pressure on the development of small molecule medicines, which due to their ability to penetrate the brain are essential to the future of innovation in pain and addiction.”⁴⁵

44. D Thomas & C Wessel (2023). *The State of Innovation in Pain and Addiction*, BIO Industry Analysis, p. 1.

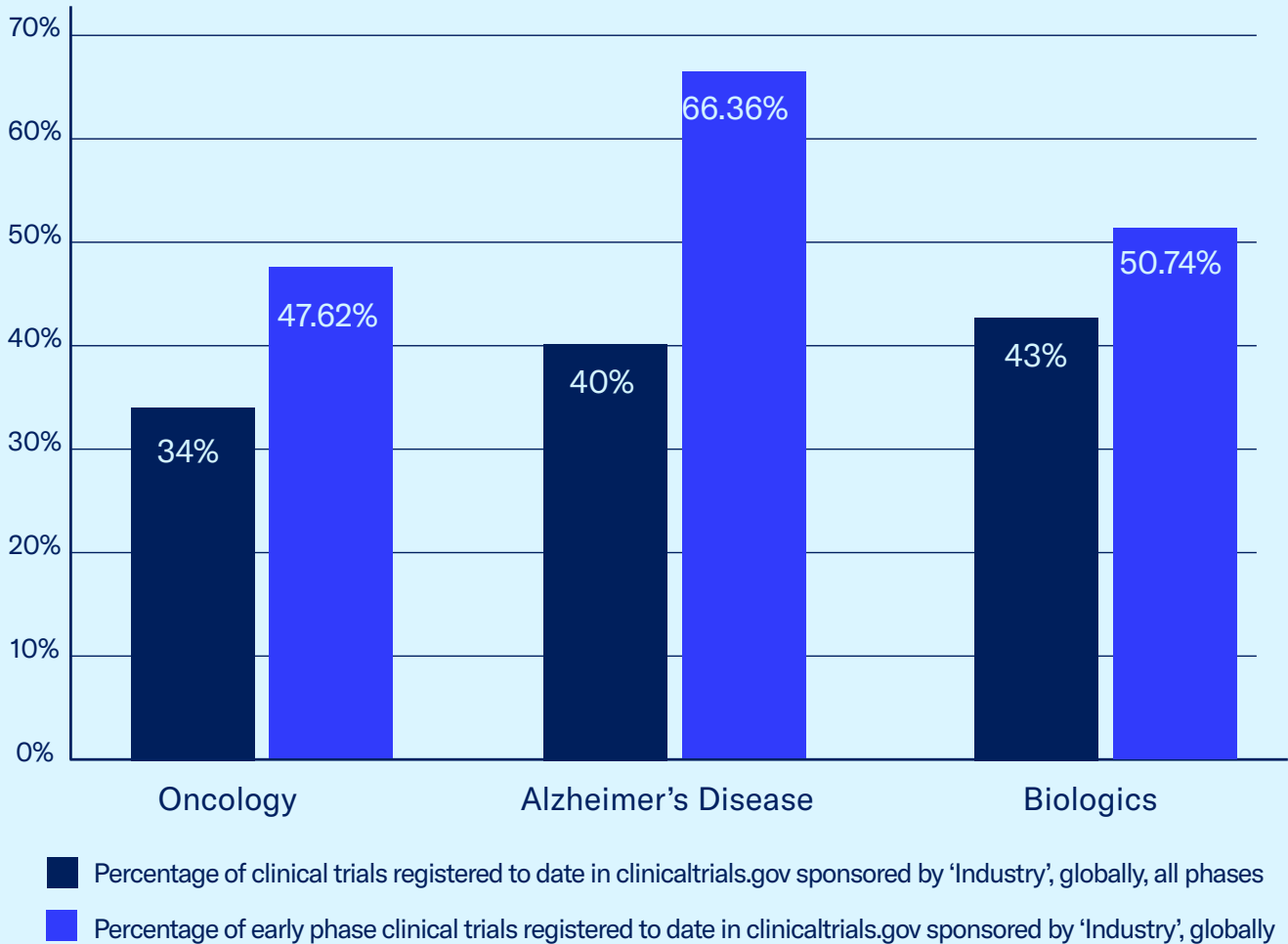
45. *Ibid.* p. 19.

Industry Sponsorship of Clinical Research

This report also collected data on industry sponsorship of clinical trials related to biologics, cancer research, and Alzheimer's

disease. Figure 32 shows the results for both early-phase trials and all clinical phases.

Figure 32: Percentage of Clinical Trials Related to Biologics, Cancer Research and Alzheimer's disease Registered to Date in clinicaltrials.gov Sponsored by industry, Globally, All Phases and Early-Phase Research



As Figure 32 shows, industry sponsorship is a key driver of investment in all phases of life sciences clinical research globally: industry sponsors 34% to 43% of all phases of clinical trials related to biologics, cancer research, and Alzheimer's disease. This

percentage increases substantially when isolating and examining only early-phase research. Industry sponsors a substantial proportion—between 47.6% and 66.4%—of early-phase research related to biologics, cancer research, and Alzheimer's disease.

Estimating Potential Losses in Clinical Trials and Life Sciences R&D Due to the IRA

As the data presented in the preceding section demonstrate, the United States has historically been the global leader in all types of clinical research. More importantly, in areas of cutting-edge, riskier, early-phase trials and research related to cancer, Alzheimer’s disease, diabetes, obesity, and biologics, the United States has accounted for an even larger proportion of clinical research. Tables 2 and 3 summarize the findings of the trials data analyzed in the

preceding section and compares the per capita number of trials for the United States and the average for the nine OECD economies across all therapeutic areas and phases of clinical research mapped. Table 2 compares clinical trials across all phases of research, and Table 3 shows clinical research related to early-phase research.

Table 2: Number of Clinical Trials Registered to Date in clinicaltrials.gov Per Million Population, All Therapeutic Areas Sampled, All Phases, United States versus Average OECD Sample

	No. of clinical trials registered to date in clinicaltrials.gov per million population	No. of oncology clinical trials registered to date in clinicaltrials.gov per million population	No. of Alzheimer Disease clinical trials registered to date in clinicaltrials.gov per million population	No. of diabetes clinical trials registered to date in clinicaltrials.gov per million population	No. of obesity clinical trials registered to date in clinicaltrials.gov per million population	No. of biologic clinical trials registered to date in clinicaltrials.gov per million population	No. of cardiovascular disease clinical trials registered to date in clinicaltrials.gov per million population
Average OECD sample	305.3	83.0	3.0	13.2	4.5	34.8	44.6
U.S.	485.9	131.7	5.0	21.1	14.6	49.6	50.9
% difference	59.15%	58.72%	65.41%	59.97%	221.97%	42.29%	13.96%

Table 3: Number of Clinical Trials Registered to Date in clinicaltrials.gov Per Million Population, All Therapeutic Areas Sampled, Early-Phase Research, United States versus Average OECD Sample

	No. of early phase clinical trials registered to date in clinicaltrials.gov per million population	No. of early phase oncology clinical trials registered to date in clinicaltrials.gov per million population	No. of early phase Alzheimer Disease clinical trials registered to date in clinicaltrials.gov per million population	No. of early phase diabetes clinical trials registered to date in clinicaltrials.gov per million population	No. of early phase obesity clinical trials registered to date in clinicaltrials.gov per million population	No. of early phase biologic clinical trials registered to date in clinicaltrials.gov per million population	No. of early phase cardiovascular disease clinical trials registered to date in clinicaltrials.gov per million population
Average OECD sample	85.0	38.2	1.1	2.8	0.6	13.5	7.5
U.S.	180.6	83.2	2.1	5.3	2.3	33.2	14.6
% difference	112.51%	117.99%	96.50%	85.27%	313.90%	146.40%	96.47%

As Tables 2 and 3 show, a marked difference exists in rates of clinical trial activity, with levels of research in the United States consistently higher than the OECD average. For all phases of clinical research and across all categories analyzed, the U.S. activity level is 42% to 220% higher than the OECD average. Significantly, this disparity only grows when examining early-phase research, with the U.S. activity level 85% to 313% higher than the OECD average.

This leadership in clinical research and developing medicines and life sciences technologies of the future risks being undermined by the IRA and the introduction of national price controls.

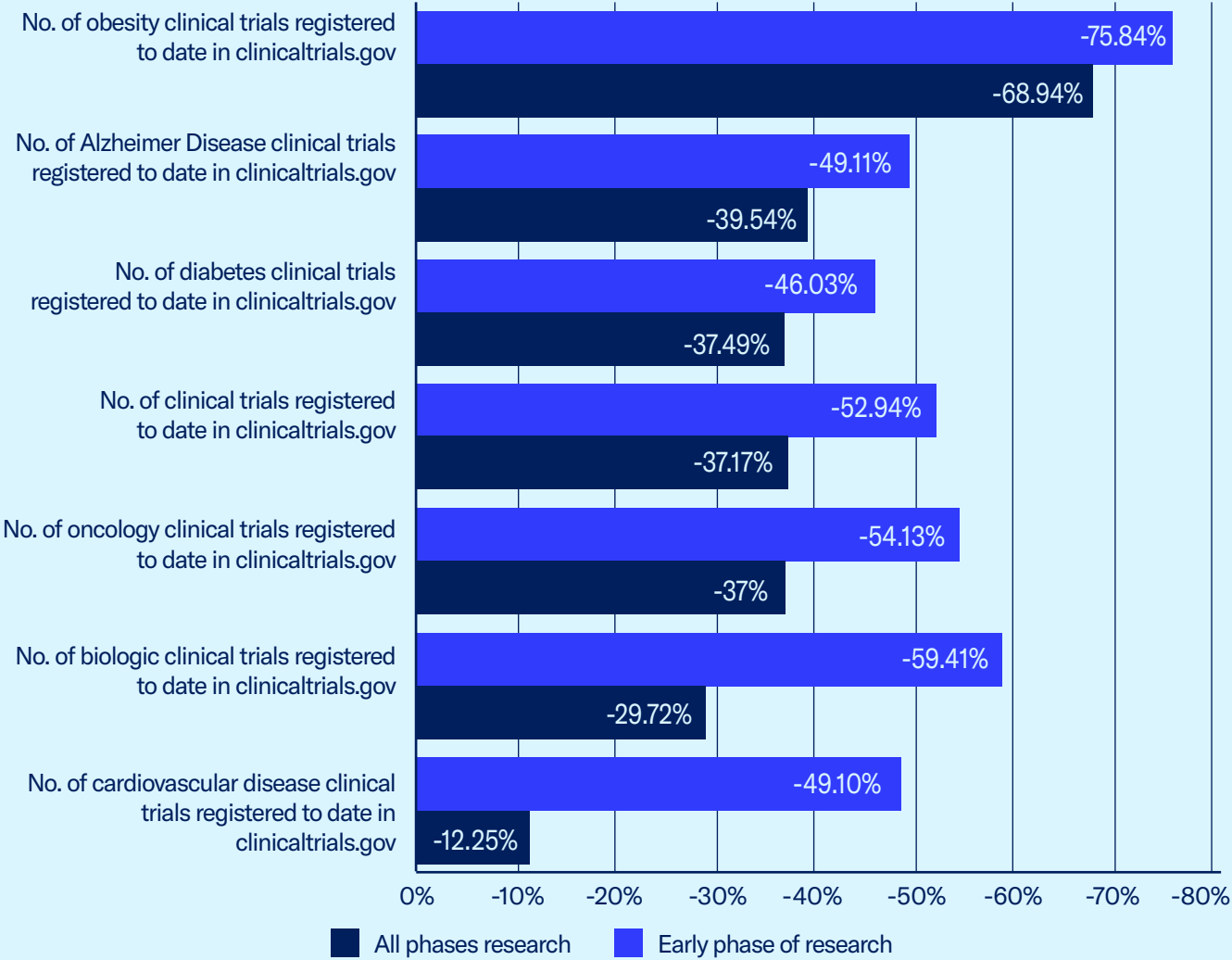
The following subsections estimate what this negative impact will be and quantify the impact on clinical trials in the United States both on an aggregate basis and for the individual areas of clinical research examined (cancer, Alzheimer’s disease, diabetes, obesity, cardiovascular disease, and biologics).

Modeling the Negative Impact of the IRA on U.S. Clinical Research Activity

By comparing levels of clinical research standardized for population size in the United States and the average for the nine comparator OECD economies, it is possible to model and provide an approximation of the potential direct and indirect negative impacts of the IRA.⁴⁶ The underlying assumption being that if the United States, through the IRA, over time adopts a national price control and life sciences cost-containment model similar to that of the sampled OECD

economies, it is not improbable to expect that over the medium to long term, this will also result in a reduction in levels of life sciences R&D and, specifically, clinical research in the United States to a similar level as the sampled OECD average. Figure 33 provides an estimate of what such a reduction expressed as a percentage would look like across all phases of research and for clinical research related to cutting-edge, early-phase research.

Figure 33: Estimated Percentage Reduction for Clinical Trials in the United States



46. In the preceding section of the report, the nine OECD comparator economies' clinical trials were aggregated, and an average number was calculated. National clinical research activity in the United States and the nine OECD comparator economies was also standardized to control for differences in population size.

As Figure 33 shows, a decline in life sciences research and clinical trials activity in the United States to the sampled OECD average would result in a future reduction in all categories of clinical research analyzed. Depending on the therapeutic field, this reduction could amount to between 12.25% (cardiovascular diseases) and 68.94% (obesity). Trials related to future early-phase research risk would be reduced by close to 50% or more with, for example, research related to biologics and cancer reduced by 59.41% and 54.13%, respectively. Early-phase research related to obesity could be reduced more than over 75%.

It is also worth noting that even in research areas that are projected to see a relatively smaller decrease in, for example, research related to cardiovascular diseases, the absolute number of patients and clinical trial participants potentially affected by a contraction in rates of such research is substantial. Given that heart disease caused an estimated 695,000 deaths in the United States in 2021—about 20% of the total—even a small decrease in the rate of clinical research and R&D related to cardiovascular diseases would affect a large pool of patients in the United States.⁴⁷

Likewise, within these categories of research, individual products and types of products may experience an even more severe contraction in R&D and clinical research. For example, with respect to orphan drugs and rare diseases, given the IRA provides only a narrow exclusion from negotiation for such related products, this may inhibit future investment and innovation in what is already a highly challenging area of pharmaceutical research. Similarly, the fact that small-molecule medicines are subject to mandatory negotiations at an earlier life cycle stage is more likely than not to have an outsized impact on levels of investment and R&D in such products.

47. CDC (2023). “Heart Disease Facts,” National Center for Chronic Disease Prevention and Health Promotion, Division for Heart Disease and Stroke Prevention.

Conclusion:

From World Leadership in Groundbreaking Innovation to the Emergence of Research Deserts—the IRA’s Negative Impact on Clinical Trials Activity in the United States

*“Where the art of medicine is loved,
there is also love for humanity.”*

—Hippocrates

The imposition of national price controls and life sciences expenditure controls is not free of cost. Price controls and life sciences cost-containment policies have a direct impact on the availability of new, innovative medicines and medical technologies for patients and consumers in the affected market. Economies that impose price controls and life sciences cost-containment policies tend to see fewer medicines introduced in the market, and patients must wait longer to access new, innovative medicines and medical technologies. But beyond access to new medicines and life sciences technologies, such policies also directly undermine future R&D investment and the development of new medicines. With fewer resources, it stands to reason that life sciences manufacturers will have less to invest in R&D and will be less likely to develop new life sciences products and services at the same rate as in the past. This logic holds true whether a new medicine was developed by a public or private research entity.

As the data presented in this document show, the United States has historically been the global leader in all types of clinical research, with strengths in areas of cutting-edge, riskier early-phase trials and research related to cancer, Alzheimer’s disease, diabetes, obesity, cardiovascular diseases, and biologics. Although this leadership in life sciences innovation is a result of many enabling factors, including scientific capacity, R&D infrastructure, human capital, strong IP protection, and a sophisticated technology transfer framework, one of the strongest drivers of innovation in life sciences has been the existence of a relatively free market in the pricing of life sciences.

The IRA and the imposition of national price controls and cost-containment measures on the biopharmaceutical sector jeopardizes much of this research leadership and the future innovation that comes with it.

As the modeling in this report suggests, clinical research related to cancer, biologics, Alzheimer’s disease, diabetes, obesity, and cardiovascular disease all risk seeing a substantial drop in rates of clinical trials. Most alarmingly, this drop is pronounced with respect to the next generation of life sciences treatments in cutting-edge, early-



phase research. This will, per definition, result in less innovation and fewer new medicines and life sciences treatments.

As the federal government moves forward with its plans for implementing the IRA, it should pause and consider the full ramifications of its proposed policies. All health systems struggle with rising costs; this is not a uniquely American phenomenon. But the solution is not to impose a “take it or leave it” system of price controls targeting medicines that will, inevitably, undermine the ability of our life sciences innovation ecosystem to continue to function at such a high level. The COVID-19 pandemic highlighted the importance of having an advanced research-based life sciences industry. Today, more than 2,000 active clinical trials are taking place globally to test treatments and potential vaccines for COVID-19. At more than 15 billion doses produced, the global manufacturing and supply of COVID-19 vaccines today outstrip global demand. A range of inpatient and outpatient treatments and therapies are available to patients today that were not

on the market at the beginning of the outbreak. It is impossible to overstate the enormity of these accomplishments. The speed at which this research has taken place is unprecedented. It shows the extensive scientific capacity developed by the life sciences and biotech communities and their ability to understand and develop a treatment for a novel virus that, before 2019, was not present in human beings, and to scale up manufacturing quickly and decisively. At scientific, manufacturing, distribution, and organizational levels, what the industry together with its partners in academia and the public sector has been able to achieve is remarkable. As many pointed out, when the FDA authorized the first vaccine for emergency use, it truly amounted to a modern-day miracle. Yet the scientific and technological capacity that has allowed industry, public research organizations, and academic researchers to achieve this technological miracle is based on decades of scientific study, innovation, and billions of dollars in sustained R&D investment. It is highly doubtful that in a post-IRA world this capacity will remain in place.