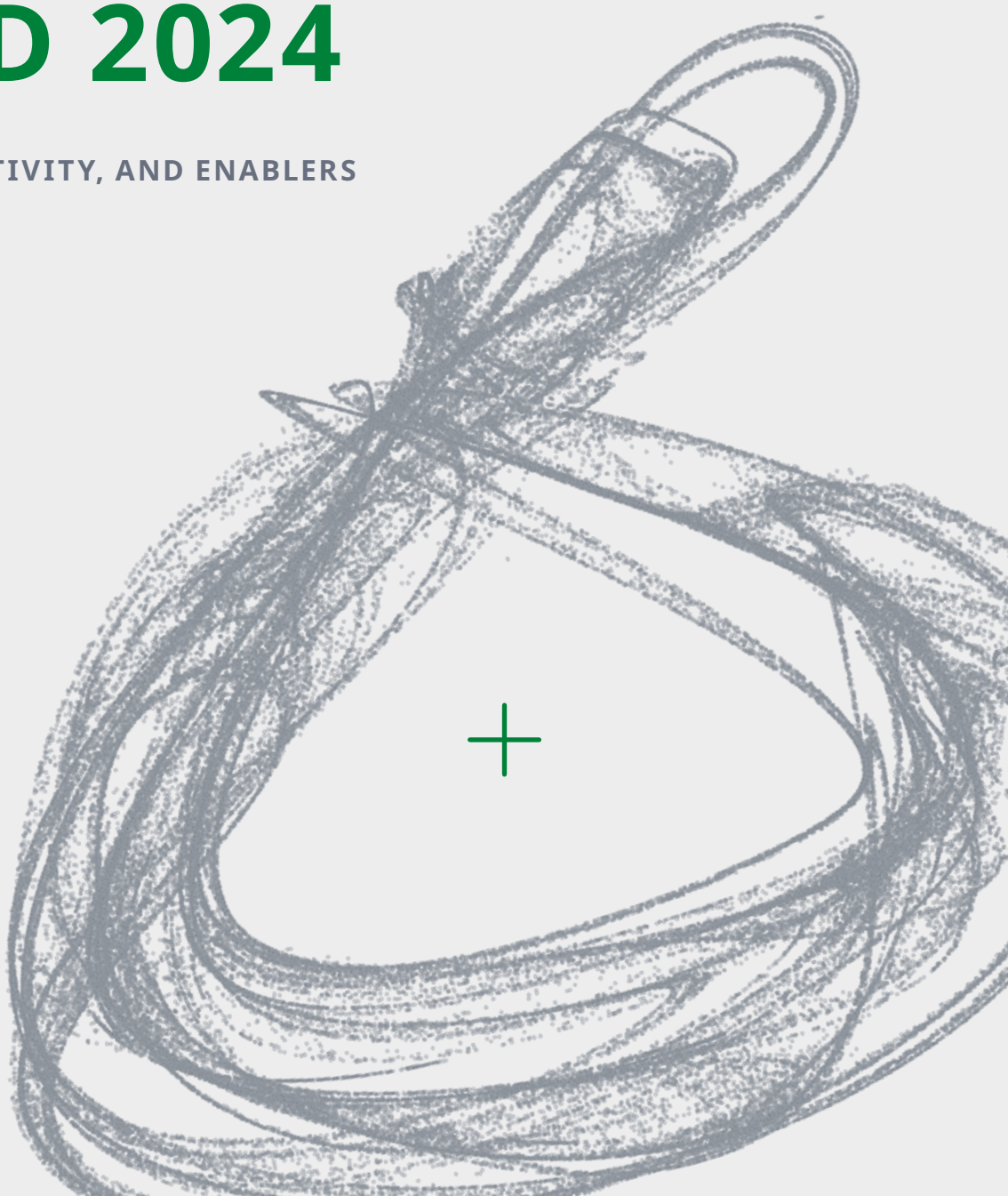
IQVIA INSTITUTE
FOR HUMAN DATA SCIENCE

Global Trends in R&D 2024

ACTIVITY, PRODUCTIVITY, AND ENABLERS



FEBRUARY
2024

Introduction

Biomedical advances are transforming healthcare globally. The multi-stakeholder ecosystem that enables this progress has been buffeted by the global COVID-19 pandemic and is resetting and refocusing on future opportunities to advance the understanding of human biology and disease, discover and develop new therapeutics, and provide evidence of the clinical value of these innovations — for individual patients, populations, and health systems. By all of the traditional metrics, including funding levels, numbers of trial starts, drug launches, R&D success rates, and many others, it is clear that industry and investors continue to see tremendous value in the vast array of ongoing research programs around the world.

This report assesses the trends in new drug launches and the overall number of initiated clinical trials. It also profiles the state of R&D funding and the activity of companies of different types. The results of research are compared to the input effort in a Clinical Development Productivity Index. The notable acceleration and adaptability of the innovation ecosystem is examined in terms of several enablers of R&D productivity, including the relationship between shortening trial durations and the 'white space' within clinical development timelines that have been reducing for some diseases and increasing for others.

The research included in this report was undertaken independently by the IQVIA Institute for Human Data Science as a public service, without industry or government funding. The analytics in this report are based on proprietary IQVIA databases and/or third-party information and are not derived from proprietary sponsor trial information.

The contributions to this report from Mohit Agarwal, Taskin Ahmed, Chris Bamford, Vaibhav Bhalotia, Tanya Bhardwaj, Lucy Haggerty, Julia Kern, Bhagyashree Nawar, Urvashi Porwal, Tanushree Thakur, and dozens of others at IQVIA are gratefully acknowledged.

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MURRAY AITKEN
Executive Director
IQVIA Institute for Human Data Science

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Source: IQVIA Institute for Human Data Science. Global Trends in R&D 2024: Activity, Productivity, and Enablers. February 2024. Available from www.iqviainstitute.org

Overview

R&D FUNDING

R&D funding levels have rebounded in 2023 after a steep decline from the peak seen in 2020-21. While the number of deals has fallen, high profile and high value deals indicate robust interest from investors and innovators in the next generation of therapies. Biopharma funding levels rebounded to $72Bn in 2023, up from $61Bn in 2022, although still well below the levels in 2020-21. M&A activity jumped to $140Bn from $78Bn in 2022, while median deal value dipped for the second year. The leading deal and M&A activity areas related to antibody drug conjugates accounted for 47% of disclosed M&A deals valued over $2Bn and 85% of large oncology deals. Deals involving China-based companies remained significant and AI deals more than doubled. R&D expenditure reported by large pharma corporations totaled a record $161Bn in 2023, an increase of almost 50% since 2018, and historically high at 23.4% of net sales for those companies.

CLINICAL TRIAL ACTIVITY

Trial starts have slowed to below pre-pandemic levels, reflecting fewer COVID-19activity and shifting research priorities. Clinical trial starts declined 15% in 2023 compared to the prior year and were down 22% from 2021 which included the peak of COVID-19-related trial activity. The three main drivers accounting for the slowdown were fewer COVID-19 trial starts, fewer non-COVID-19 starts by larger companies, and fewer by emerging biopharma companies. Trial starts from China-headquartered companies have risen to 28% of trial starts, up from 3% a decade ago, and an increasing proportion of Chinese companies have had international trial starts contrasted with the domestic-only activity of most firms.

The top four diseases in terms of trial starts — oncology, immunology, metabolic/endocrinology, and neurology — account for 79% of trial starts and declined less than other diseases. Rare disease trial activity remains high and slowed less than trials focused on larger populations. The disease focus of rare disease research is predominately in oncology while diseases with larger populations study a wider variety of diseases. Novel oncology mechanisms, especially cell and gene therapies, ADCs and multi-specific antibodies, have risen to 25% of oncology trials. Industry sponsored cell and gene therapy trials have more than tripled over the last decade while non-industry have grown 5%. CAR T-cell therapy clinical research is focused on oncology, while other diseases may benefit from other cell and gene modalities.

Obesity clinical trials in 2023 were up 68% from 2022 and have nearly doubled when compared to five years ago, including 124 drugs in active development, 40% of which are GIP/GLP glucagon receptor agonists and 46% of which have oral formulations in development. Neurology research is focused on Alzheimer's, Parkinson's, and epilepsy, with a range of other often rare diseases. Depression trial starts were 25% lower in 2023 than pre-pandemic with psychedelics being tested in nearly 40% of the 2023 trial starts. Infectious disease trials slowed to below pre-pandemic levels from both COVID-19 trials and other infection targets, and a significant reduction in trials starts for antibacterials.

NEW DRUG APPROVALS AND LAUNCHES

A total of 69 novel active substances (NASs) were launched globally in 2023, up six from the prior year and representing a return to pre-COVID-19 trends. A total of 362 NASs have launched globally in the past five years, bringing the 20-year total to 942. An increasing gap exists between countries such as the U.S., with 267 NAS launches in the past five years, and the EU4+UK with 182, and China, which becomes the second largest with 192. While the number of NAS launches in China is rising, an increasing number are not available in other countries, reflecting both a rising domestic industry and a mix of reduced barriers and rising incentives for multinational NAS launches. Global NAS launches excluding China-only NASs were 52 in 2023, up one from 2022.

Industry-wide clinical development productivity rose primarily due to improved success rates, which rose from historic lows to the highest level since 2018. Efforts to manage trial complexity and durations have had more mixed results.

There is a rising gap in terms of the drugs launched in the U.S. and those available to patients in the largest European countries, with 113 drugs (42%) launched in the U.S. in the past five years that are not in Europe, while there are only 11 (6%) European launches not in the U.S.

First-in-class NAS launches continue to emerge from research, including six first-in-class cell and gene therapies launched in 2023, along with firsts in menopause, neurology, and oncology. Emerging biopharma companies originated 56% of all new drugs in 2023 and launched 53% of them, less than in recent years but still more than the first half of the decade.

CLINICAL DEVELOPMENT PRODUCTIVITY

Industry-wide clinical development productivity rose primarily through better success rates, which rose from historic lows to the highest level since 2018. Clinical development productivity reached an index level of 17.4 against a baseline of 20 in 2010, and continuing a rebound from the low of 12.8 in 2021. Most of the productivity increase in 2023 was driven by an increase in success rates, which rose to 10.8% in 2023, almost doubling from lows in 2022 of 5.9%. Composite success rates were lifted by increased rates in Phase I, Phase III and regulatory review, and varied across disease areas with significant increases in oncology and rare diseases.

Clinical trial complexity increased in 2023, returning to levels seen in 2020 but with variations among the five elements of complexity measured. The declining number of countries and sites for rare diseases and oncology trials was a key driver of the decrease in overall complexity. The average number of countries in trials has been declining, more markedly in Phase II and III studies, and including a marked shift to single-country studies even in later phases and rationalization to fewer countries in multi-country studies. Emerging biopharma are running more single country trials than large pharma with China trials driving recent trends.

Another key element of productivity is duration, and trial durations have declined while the 'white space' before starting a subsequent research phase has increased, resulting in overall increases in development timelines. Nineteen drugs were launched less than five years into their patent terms in the past four years, up from eight in total in the six years from 2014 to 2019. Median overall development duration was two to four years faster when expedited regulatory pathways were used, and is generally shorter for biologics, orphan, and specialty drugs, an important feature as these pathways and drug types have increasing share of new drug launches.

PRODUCTIVITY ENABLERS

Industry sponsors are responding to therapeutic and regulatory shifts and opportunities with a range of strategies and approaches designed to enhance or enable productivity. Regulatory agencies are generally undergoing positive changes across geographies, addressing transparency, flexibility, harmonization, speed, and simplicity, but capacity constraints are delaying implementation of consistent approaches in some geographies.

Large pharmaceutical companies generally run trials with more countries and sites, and their country utilization over the decade is evidence of ongoing and evolving analytical focus to optimize clinical trial footprints. Declining inclusion of Black/African American and Hispanic patients in the U.S. and global clinical trials over the last three years reflects challenges of a shifting therapeutic and geographic footprint and ongoing need for integrated trial planning.

Clinical program design strategies, including use of predictive biomarkers, real-world evidence, single-arm trials, and combined-phases, can contribute to shorter development durations. Novel trial designs have averaged 18% of trials since 2020, led by oncology, with more than 29% novel designs, and these studies can contribute to slower initial development but faster and greater overall program success. Decentralized methodologies remain a stable feature of trial activity, albeit at a lower level after the COVID-19 driven peak in 2020.

Clinical development programs resulting from AI utilization in discovery are maturing with an increased number of late-stage programs and examples of new indications for exiting drugs, but are still to deliver a novel active substance to the market.

Industry has been focused on minimizing regulatory setbacks in the form of complete response letters (CRLs), especially for clinical reasons, although overall rates were higher in 2023. Operational or non-clinical reasons for CRLs have been impacting emerging biopharma companies differently than larger firms.

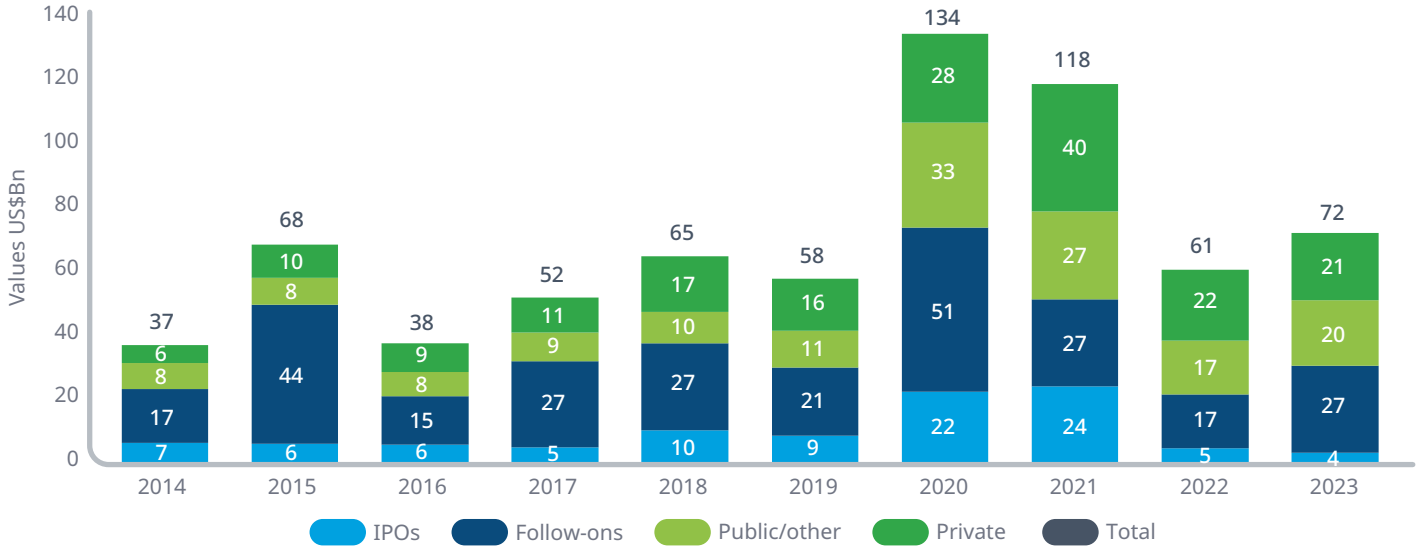
R&D funding

- Biopharma funding levels rebounded to $72Bn in 2023, up from $61Bn in 2022, although still well below the levels in 2020/21.
- M&A activity has jumped to $140Bn from $78Bn in 2022 while median deal value dipped for the second year.
- Deals between pharma companies dropped by 14% from 2022 to 2023, mostly from deals involving EBP companies.
- High profile deals involving Chinese companies included multiple antibody drug conjugates and both inward and outward deals.
- The leading deals in 2023 included 11 deals over $5Bn and focused on cancer, neurology and cardiovascular.
- There were six deals related to antibody drug conjugates (ADCs) totaling $90Bn in deal value, representing 45% of the overall $200Bn related to the 31 deals valued above $2Bn each.
- More than $12Bn in life sciences deals with AI, machine learning, or advanced analytics were announced in 2023, more than double the level in the prior two years with the value per deal jumping to $98Mn from an average of $27Mn in the prior three years.
- R&D expenditure by large pharma corporations totaled a record $161Bn in 2023, an increase of almost 50% since 2018 and historically high at 23.4% of companies' net sales.

R&D funding levels have rebounded in 2023 after a steep decline from the peak of the pandemic. While the number of deals has been falling, high profile and high value deals indicate robust interest from investors and innovators in the next generation of therapies.

Biopharma funding levels rebounded in 2023 despite fewer IPOs

Exhibit 1: Biopharma funding levels US$Bn, 2014–2023



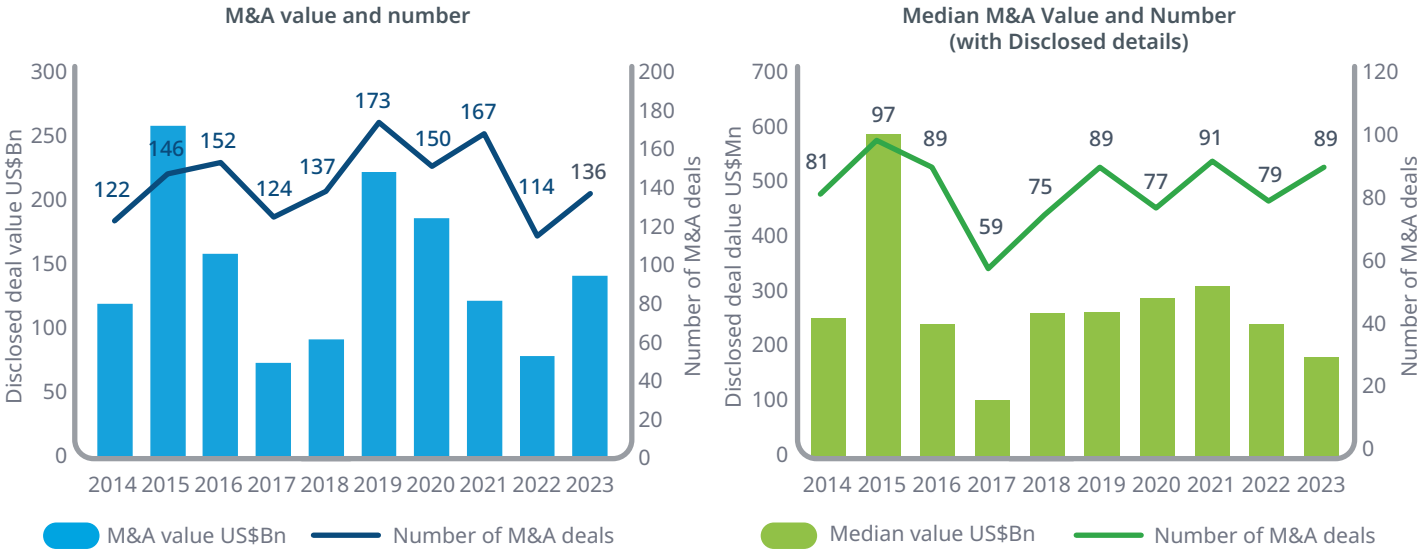
Source: BioWorld, Jan 2024.

- Biopharma funding, including IPOs, follow-on funding, and venture capital investment, rebounded in 2023 after a sharp slowdown in 2022 from the heightened levels during the pandemic.
- The level of activity still exceeds the 2019 level, although the mix of funding types has shifted, and IPO activity was notably lower.
- The shifts in deal activity reflect changes in the types of companies being invested in, their therapeutic focus, and where they are located.
- Start-ups with a focus in COVID-19 had seen funding expand during 2020 and 2021 but slowed in the most recent year.
- In 2023 alone, follow-on funding represented about 38% of biopharma funding, for which 91% was comprised of companies headquartered in the U.S.
- Companies headquartered in China and Europe have seen deals slow more dramatically than those in the U.S., decreasing by 59% and 74%, respectively.

Notes: IPO means initial public offering; Follow-on refers to a public offering of shares that is not the first one; Public/other financings are when public companies receiving financing in some other way; Private means venture capital investments.

M&A activity has rebounded overall with deal value and deal counts rising, while median deal value dipped for the second year

Exhibit 2: Biopharma M&A Activity US$Mn, 2014–2023



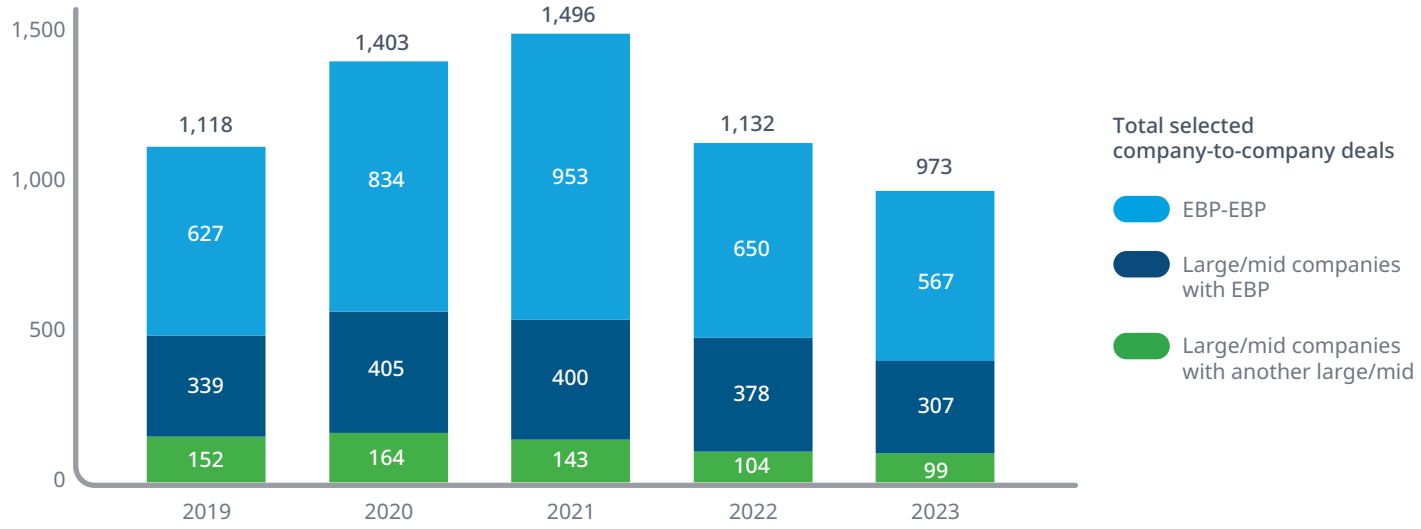
Source: BioWorld, Jan 2024.

- M&A deal values rebounded to $140Bn in 2023 from a low in 2022 but have not yet reached the levels seen in 2019 and 2020.
- Similarly, the number of M&A deals have slowly decreased since 2019, with an uptick to 136 deals in 2023.
- Although the median disclosed deal value in 2023 of $175Mn was 42% below the $301Mn in 2021, the aggregate deal value increased driven by some very high value deals.
- High profile M&A deals were led by Pfizer and Seagen for $43Bn focused on oncology antibody drug conjugates (ADCs). Another landmark M&A deal in 2023 was between AbbVie and Immunogen for $10.1Bn, which also led to the acquisition for a first-in-class antibody drug conjugate (ADC) in oncology. In the same year, BMS acquired RayzeBio for $4.1Bn (Exhibit 5).
- Deal value is the disclosed value of the deal when announced; for 2023 alone, the number of disclosed deals represent 65% of total M&A deals.
- For the past five years, the number of non-disclosed M&A deals represent 43% of total M&A deals, which if valued at the median deal value in the year they occurred, would add $81Bn (14%) to the disclosed $743Bn for an estimated total value of $851Bn over five years (not shown).

Notes: M&A is involving at least one biopharmaceutical company. Deal value is the disclosed value of the deal when announced.

Deals between pharma companies dropped by 14% from 2022 to 2023, mostly from deals involving EBP companies

Exhibit 3: Number and share of deals by company segment, 2019–2023



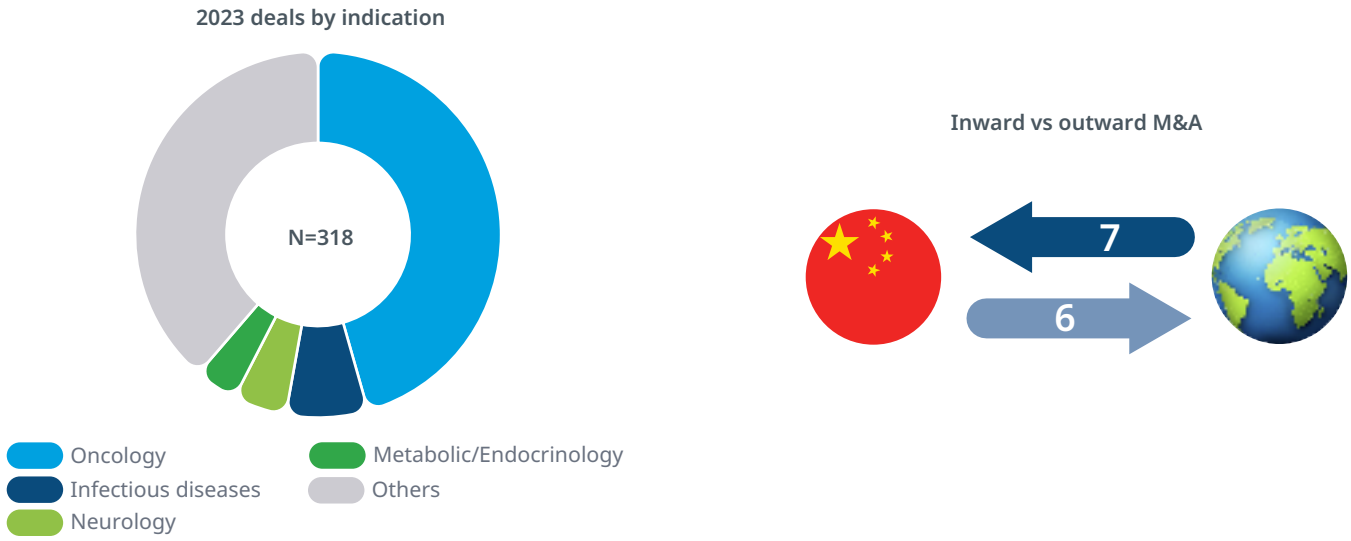
Source: IQVIA Pharma Deals, Dec 2023.

- Emerging biopharma companies (EBPs) — defined as those with less than $200Mn in R&D spending and less than $500Mn per year in annual revenue — have expanded their involvement in deals steadily over the past five years, with a slight dip in 2023.
- In 2019, large and-mid-sized companies — those with more than $5Bn in global revenue — were involved in 44% of deals that involved other large and mid-sized or emerging companies; while that share of the company deal activity has remained steady, as a level of deals of the company, it has dropped to 406.
- The shifts in activity over the past five years have meant that 74% of all deal activity between these types of companies involves an emerging company, even as the activity between emerging companies without a larger firm now represent 66% of deals.
- The rising independence of emerging biopharma companies in recent years started to shift in 2021 as the share of deals involving larger companies jumped from 30% in 2021 to 35% in 2023.
- Novel drugs developed by emerging biopharma are also being launched by them less than in recent years, with 53% of the 26 EBP-originated NAS launches in the U.S. in 2023 also being launched by an EBP (Exhibit 31).

Notes: Deals in this analysis are excluding non-funding deals. Funding deals are deals that involve research grants or funding from govt institutions, govt bodies, universities or other academic institutions. Excluding VC and Funding Grants from Non-Commercial. Excludes deals where one side is not a pharmaceutical company. Emerging biopharma (EBP) are defined as companies with <$500Mn of prescription pharmaceutical sales and <$200Mn of R&D spend.

High profile deals involving Chinese companies included multiple antibody drug conjugates, and both inward and outward deals

Exhibit 4: Overview of China-focused deal activity in 2023



Source: IQVIA Pharma Deals, Jan 2024.

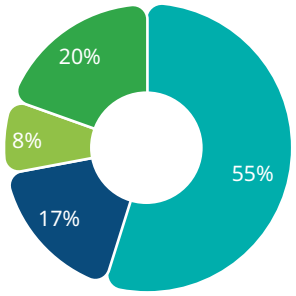
- In 2023, 318 deals were announced relating to China, either with the main or target company being Chinese headquartered.
- There was a significant focus in oncology, accounting for 46% of deals, in contrast to overall deal activity where oncology represents 31%.
- Infectious diseases represent 7% of China deal activity, while neurology was 5% of the deals, closely following the overall deal activity of 8% and 6%, respectively.
- While many of the deals relating to China are between Chinese companies, there is a notable pattern of both inward (international companies doing deals with Chinese companies) and outward deals (Chinese firms acquiring or doing deals with external companies), especially in the U.S.
- There are likely more deals involving Chinese companies that won't disclose details to enable identification of the value and/or disease or therapy area; recent efforts by the U.S. Securities and Exchange Commission (SEC) have been made to encourage more disclosures.[1]
- Most notable disclosed deals involving Chinese companies focus on oncology antibody drug conjugates (ADCs); the collaboration between Eisai and Blissboi can reach $2Bn, BioNTech and Duality Biologics could reach $1.5Bn, and Merck KGaA's collaboration with Jiangsu Hengrui Pharmaceutical can total €1.4Bn.

Notes: Companies with China headquarters and deals disclosing phase and therapy/disease focus have been included. Inward signifies foreign companies doing deals/acquiring Chinese companies and outward represents Chinese companies doing deals/acquiring foreign companies.

The leading deals in 2023 included 11 deals over $5Bn and focused on cancer, neurology and cardiovascular

Exhibit 5: Deals with value >$2Bn in 2023 by therapeutic area

N=31 deals >$2Bn, Total $200Bn



Others (9 deals / $39Bn)	
Merck + Prometheus	10.8
Roche + Telavant	7.3
Astellas + Iveric	5.9
Novartis + Chinook	3.5
Proxygen + Merck & Co	2.6
Bausch & Lomb + Novartis (asset acq)	2.5
Lilly + DICE	2.4
Quell + AstraZEneca	2.1
Belharra + Genentech	2.1

Cardio Metabolic (6 deals / $16.8Bn)	
Alnylam + Roche	3.1
Roche + Carmot	3.1
Sanofi + Provention Bio	2.9
Valo Health + Novo Nrdisk	2.8
Aspect Biosystems + Novo Nordisk	2.7
Avidity Bioscience + BMS	2.3

Neurology (4 deals / $34Bn)	
BMS + Karuna	14.0
Abbvie + Cerevel	8.7
Biogen + Reata	7.3
Neurocrine + Voyager	4.4

Oncology (12 deals / $109.6Bn)	
Pfizer + Seagen (ADCs)	43.0
Daiichi + Merck (ADCs)	22.0
AbbVie + Immunogen (ADCs)	10.1
Systimmune + BMS (ADCs)	8.4
BMS + Mirati	5.8
BMS + Razebio	4.1
Nurix + Seagen (ADCs)	3.5
C4 + Merck & Co (ADCs)	3.1
AbbVie + Immunonome	2.8
Nanobiotix + J&J	2.8
Monte Rosa + Roche	2.1
Orionis + Genentech	2.0

Acquisition Alliance/collaboration

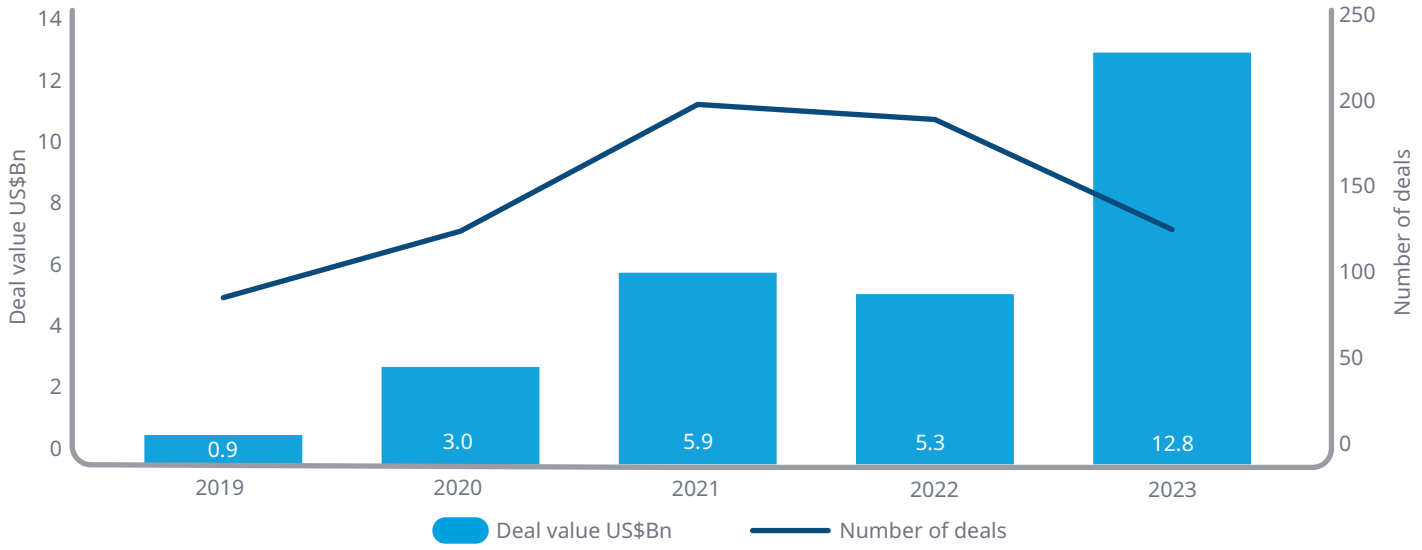
Source: IQVIA Pharma Deals, Dec 2023.

- There were 31 deals announced in 2023 with values above $2Bn and totaling $200Bn, with 55% in oncology.
- The largest cluster of deal activity was in antibody drug conjugates (ADCs) which were 6 of the 12 oncology deals and accounted for $94Bn of the $109.6Bn of oncology deal value in these larger deals.
- The largest deal across therapy areas was Pfizer's acquisition of Seagen for $43Bn, also primarily driven by ADC assets.
- Neurology represents 17% of the deal activity in 2023 with four deals for a total of $34Bn, led by BMS' acquisition of Karuna — which focuses on neurological and psychiatric therapies — for $14Bn.
- A total of six cardiology/metabolic deals represent $16.8Bn or 8% of total deal values, with the largest acquisition deal of Carmot by Roche — which includes an obesity treatment — for $3.1Bn.
- The largest collaboration deal was made in oncology between Daiichi and Merck for $22Bn for the development and commercialization of three of its candidate cancer drugs.
- For $4.4Bn, Neurocrine and Voyager collaborated to develop gene therapies for the treatment of neurological diseases.
- Another alliance was formed in cardiology/metabolic between Alnylam and Roche — involving a hypertension treatment — for $3.1Bn.

Notes: ADCs are defined as antibody drug conjugates.

Over $12Bn in life sciences deals with AI, machine learning or advanced analytics were announced in 2023

Exhibit 6: Number and value of deals with artificial intelligence, machine learning, informatics, 2019–2023



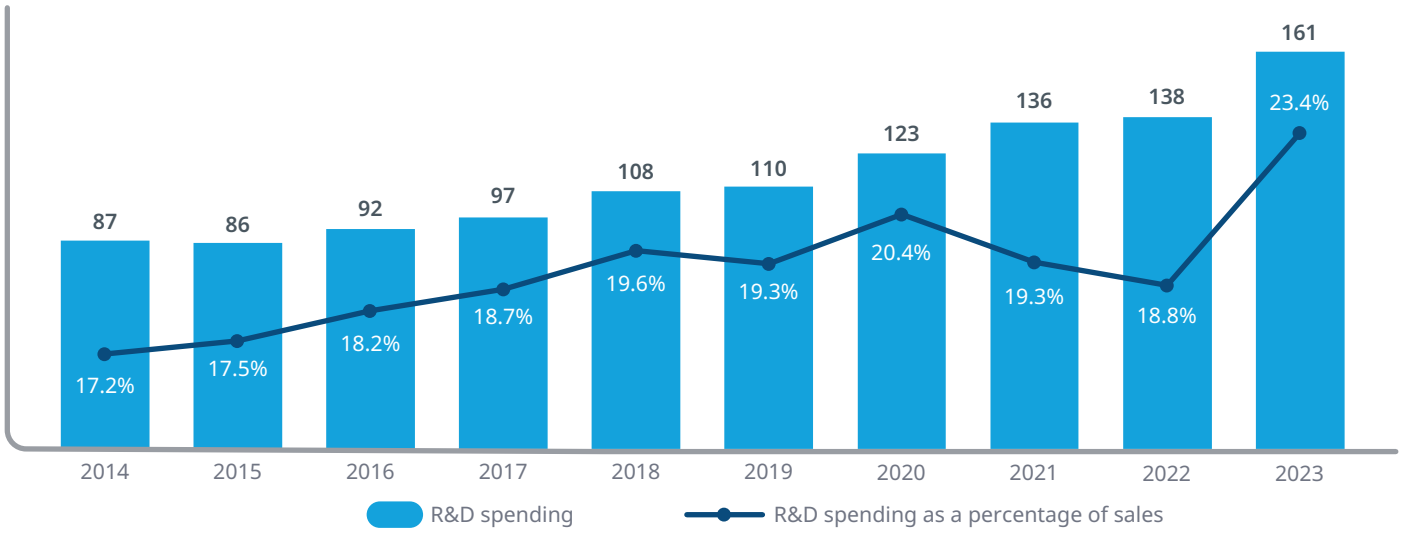
Source: IQVIA Pharma Deals, Dec 2023.

- More than $12Bn in life sciences deals with AI, machine learning or advanced analytics were announced in 2023, more than double the level in the prior two years, with the value per deal jumping to $98Mn from an average $27Mn in the prior three years.
- In 2023 alone, the worth of deals is about nine times higher than what it was in 2019 and almost four times higher than what it was in 2022; there are likely many more deals, collaborations, or uses of technology which were not disclosed.
- The largest deal disclosed in this area was between Exscientia and Sanofi to discover an artificial intelligence-driven drug for oncology and immunology for $5.2Mn; other deals include Moderna and Immatics for $1.8Mn for oncology therapeutics and Shape Therapeutics and Roche to develop gene therapies for neurodegenerative diseases (Alzheimer's, Parkinson's, dementia) for $3Mn.
- Oncology represents about 43% of AI deals in 2023 and a total of 35% of deals for the last five years.
- Advances in artificial intelligence (AI), machine learning, and other advanced analytics are increasingly being applied to the life sciences with deals announced focusing on drug discovery and patient cohort identification, among others.
- According to the FDA, in 2021, more than 100 drug and biologic application submissions used these technologies; this led to the release in May 2023 of an FDA paper for stakeholders to discuss the use of AI/ML in drugs and biological products development.[2]

Notes: The deals in this analysis include deals which referred to key search terms of artificial intelligence (AI), machine learning, informatics or advanced analytics capabilities. Not all deals of this nature have been disclosed.

R&D expenditure by large pharma corporations totaled a record $161Bn in 2023, an increase of almost 50% since 2018

Exhibit 7: Large pharma R&D spending as a percentage of sales 2014–2023*, US$Bn



Source: Company financial statements, IQVIA Institute, Nov 2023.

- The largest pharmaceutical companies together spent more than $161Bn on research and development in 2023, up $53Bn or 49% from the level five years ago (2018).
- R&D spending rose to 23.4% in aggregate across these 15 companies, a sharp increase over 2022, due in part to lower sales by this cohort as COVID-19 vaccines and therapeutics sales declined, and the accounting for acquired R&D as an expense by some companies.
- R&D expenditure and sales are as reported in company financial statements.
- R&D expenses can include write-offs of failed R&D programs developed internally or acquired, which can bring year-to-year variability in the level of total spending.
- These represent the total company view and some divisions, such as consumer health, are typically less R&D-intensive than the pharmaceutical division.

Notes: Based on financial reporting for twelve months ending Dec 31, 2023 for all companies except Amgen, Astra Zeneca, Gilead, and Eli Lilly which are based on 12 months ending Sept 30, 2023. All other years reflect total R&D for the calendar year indicated. Companies include: AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Gilead, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, and Takeda. These represent the total company view, and some divisions such as consumer health are typically less R&D-intensive than the pharmaceutical division. The total expenditure is as reported by companies in their financial statements.

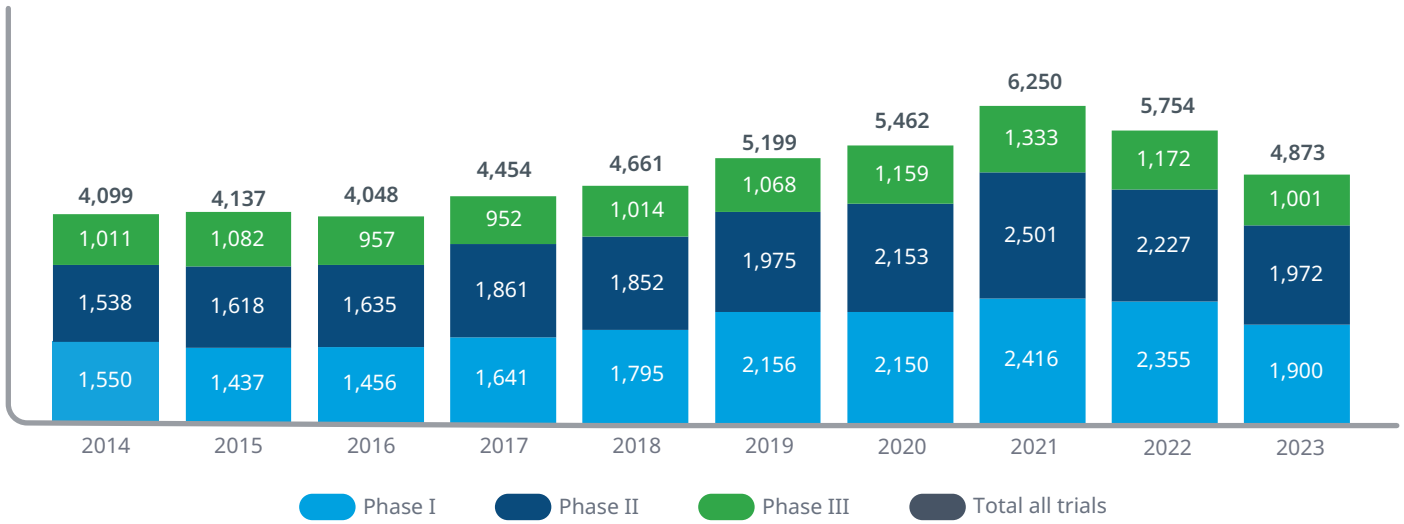
Clinical trial activity

- Clinical trial starts declined 15% in 2023 compared to the prior year and were down 22% from 2021, which included the peak of COVID-19 related trial activity.
- Emerging biopharma companies started 416 fewer non-COVID-19 trials in 2023 than they did in 2021, while larger companies started 524 fewer.
- Trial starts from China-headquartered companies have risen to 28% of trial starts, up from 3% a decade ago.
- In the past three years, more than one-quarter of Chinese companies have had international trial starts, up from 21% over the prior seven years.
- The top four diseases in terms of trial starts — oncology, immunology, metabolic/endocrinology, and neurology — account for 79% of trial starts and declined less than other diseases.
- Rare disease trial activity remains high and slowed less than trials focused on larger populations; the disease focus of rare disease research is predominately focused in oncology, while diseases with larger populations study a wider variety of diseases.
- Novel oncology mechanisms, especially cell and gene therapies, ADCs and multi-specific antibodies have risen to 25% of oncology trials.
- Industry sponsored cell and gene therapy trials have more than tripled over the last decade, while non-industry have grown 5%.
- CAR T-cell therapy clinical research is focused on oncology, while other diseases may benefit from other cell and gene modalities.
- Obesity clinical trials in 2023 were up 68% from 2022 and have nearly doubled when compared to five years ago, including 124 drugs in active development, 40% of which are GIP/GLP glucagon receptor agonists and 46% of which have oral formulations in development.
- Neurology research is focused on Alzheimer's, Parkinson's and epilepsy, with a range of other often rare diseases.
- Depression trial starts were 25% lower in 2023 than pre-pandemic, with psychedelics being tested in nearly 40% of the 2023 trial starts.
- Infectious disease trials slowed to below pre-pandemic levels from both COVID-19 trials and other infection targets, including a significant reduction in trials starts for antibacterials.

Trial starts have slowed to below pre-pandemic levels with some of the decline explained by less COVID-19 activity, while the remainder highlights shifting research priorities.

Total clinical trial starts decreased by 15% in 2023, dipping below pre-pandemic level as COVID-19 trial starts slowed

Exhibit 8: Total number of clinical trial starts by phase, 2014–2023



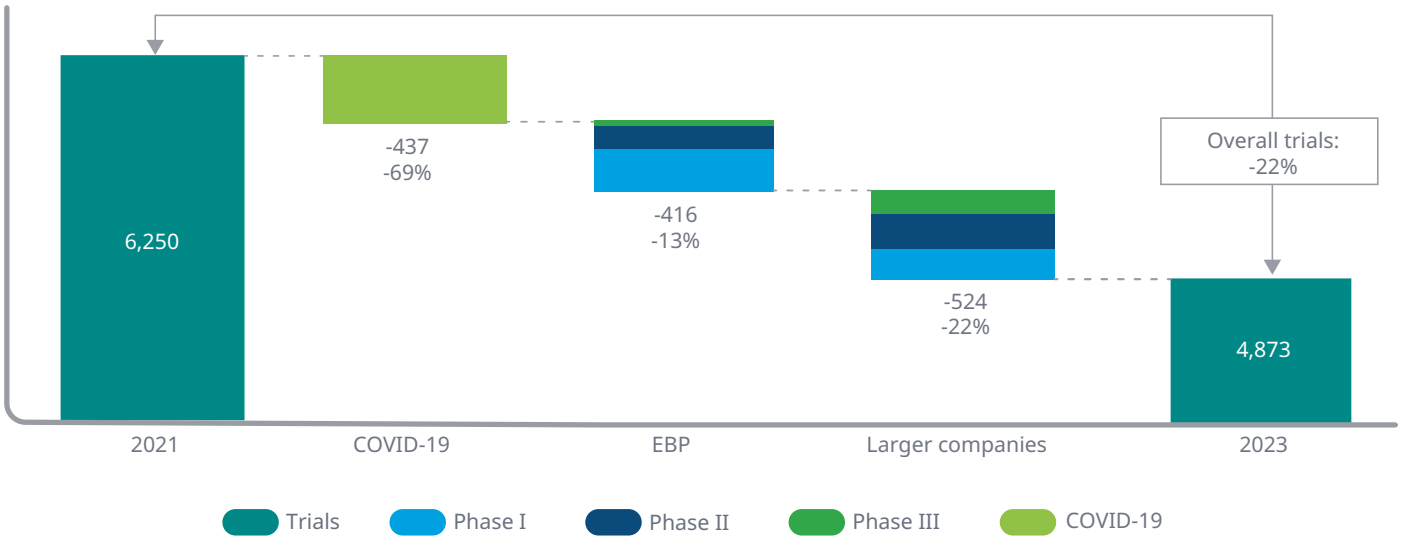
Source: Citeline Trialtrove, Jan 2024.

- Clinical trial starts slowed in 2023, with a 15% decline compared to 2022 and down 22% when compared to 2021, with 32% of the decline driven by COVID-19 trials, which have declined 69% compared to 2021 (Exhibit 9).
- Without these COVID-19 trials, trial starts have slowed to below the pre-pandemic level.
- Phase I had the most declines, with 19% fewer than 2022; Phase II activity decreased by 11% and Phase III had a 15% decline in planned or actual trial starts, matching the overall trend.
- With COVID-19 trials no longer driving trends, the reduction in starts is more driven by companies' reduced study starts with multiple and interactive drivers, including companies from key geographies such as China, with patterns visible in emerging biopharma as well as larger company segments.
- While COVID-19 disruptions have largely faded, the impact of historic delays in starts or completions will have continuing effects on companies' subsequent activities, especially for those who are more dependent on funding flows.
- It is notable that trial starts include both planned and actual starts, and not all planned trials reported here will have started by the end of the year 2023 and, accordingly, trial start trends in recent years should be interpreted with caution.

Notes: Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Terminated trials are included to track the activity still involved with their initiation, partial execution and termination. Trials were industry sponsored, interventional trials and device trials were excluded.

Trial starts declined 22% since 2021 impacting emerging biopharma more than larger companies

Exhibit 9: Change in industry interventional trials between 2021 and 2023



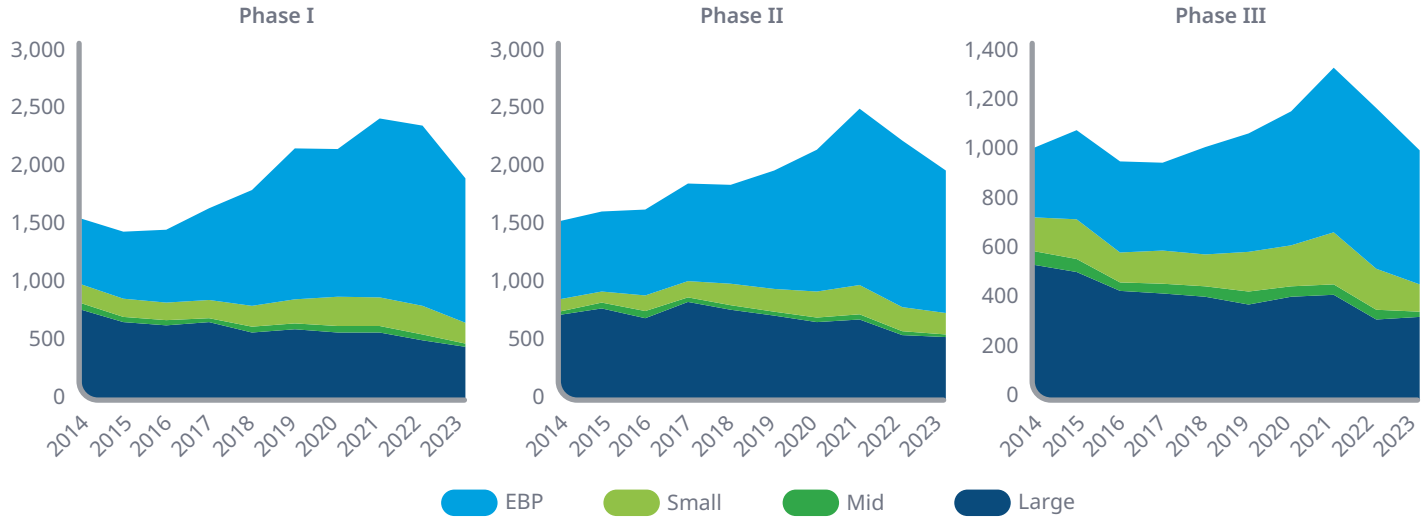
Source: Citeline Trialtrove, Jan 2024.

- Clinical trial starts declined 22% or 1,377 from 2021 to 2023, with three key drivers associated with COVID-19, emerging biopharma and larger companies.
- Emerging biopharma companies have had an overall larger impact on the slowdown as they had started more COVID-19 trials than larger companies, and their COVID-19 decline (289) was greater than the reduction by larger companies (148).
- EBP COVID-19 trial starts were down 66% to 152 in 2023, whereas larger companies are down 80% and started only 37 trials in this area in 2023.
- Emerging companies' non-COVID-19 trials were down 416 or 13%, with most of the decline in earlier phases.
- Outside COVID-19, larger companies had a larger decline, reflecting 524 or 22% fewer trial starts in 2023 than in 2021, the same as the overall market decline.
- Over half of the decline in trial starts sponsored by larger companies are associated with a decrease in multi-study clinical programs, particularly on molecules which first entered the clinic more than 10 years ago.
- Larger companies are also licensing assets later, or not at all, to manage investment risk, as seen with the larger number of EBP originated launches without a larger-company partner (Exhibit 31).

Notes: Industry interventional studies phases I,II, III. Company segment when two or more companies are involved is determined by the larger sales segment. Larger and EBP segments exclude COVID-19. Larger companies includes segments large, mid and small. Large companies are those with with global prescription sales exceeding $10 billion in the calendar year. Mid-size companies have global prescription sales between $5 and $10 billion in the calendar year. Small companies have global prescription sales between $500 million to $5 billion in the calendar year. Emerging biopharma (EBP) companies are defined as those with either R&D spend <$200 million or prescription sales up to $500 million. Multi-study clinical programs defined as 10 or more studies for the primary tested drug since 2000.

Emerging biopharma companies are responsible for two-thirds of trial starts, but declined the most since the peak in 2021

Exhibit 10: Share of clinical trial starts by phase and company segment, 2014–2023



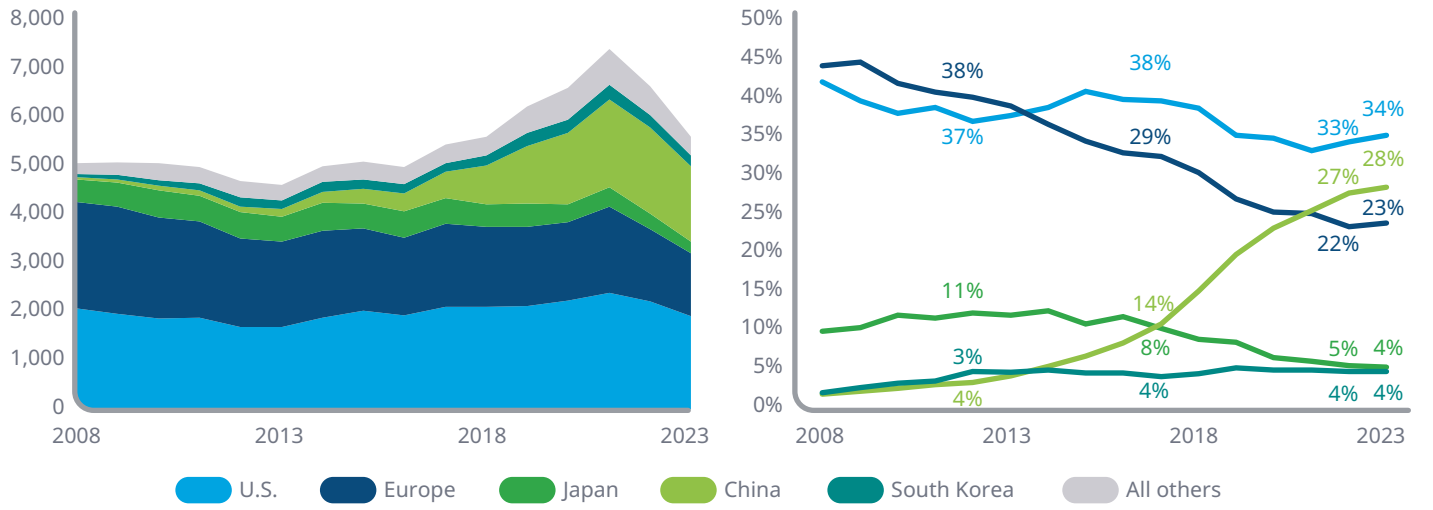
Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Jan 2024.

- The contribution of emerging biopharma companies — those with less than $500Mn in annual sales and R&D spending less than $200Mn per year — remains the largest, while large pharma companies — those with greater than $10Bn in annual sales — represent a smaller share of the trial activity.
- Large pharma companies now represent 27% of trial starts, up 3% from 2022 but down from 50% in 2014.
- Mid-sized and small companies, with revenues between $500Mn and $10Bn in annual sales, represent 11.3%, down from 12.9% in 2022 and 13% from 2014.
- EBP companies sponsored 66% of Phase I trial starts in 2023, nearly three times the 23% from large companies.
- In Phase II, EBP started 62% of studies compared to the 54% of Phase III they sponsored; in 2014, EBP companies were a smaller share of starts with 44% of Phase II and 27% of Phase III.
- Large companies started 27% in Phase II in 2023 and 33% in Phase III, both down from 48% and 54%, respectively, in 2014.
- Emerging biopharma companies have increased their share of early phase trials in the past decade; while the historic pattern for research assets to be acquired or licensed by larger companies persists, it appears that the acquisitions were happening at earlier development phases a decade ago than today.

Notes: Industry interventional studies phases I,II, III. Company segment when two or more companies are involved is determined by the larger sales segment. Large companies are those with global prescription sales exceeding $10 billion in the calendar year. Mid-size companies have global prescription sales between $5 and $10 billion in the calendar year. Small companies have global prescription sales between $500 million to $5 billion in the calendar year. Emerging biopharma (EBP) companies are defined as those with either R&D spend <$200 million or prescription sales up to $500 million.

Trial starts from China-headquartered companies have risen to 28% of trial starts from 3% a decade ago

Exhibit 11: Number of Phase I to III trial starts based on company headquarters location, 2008–2023



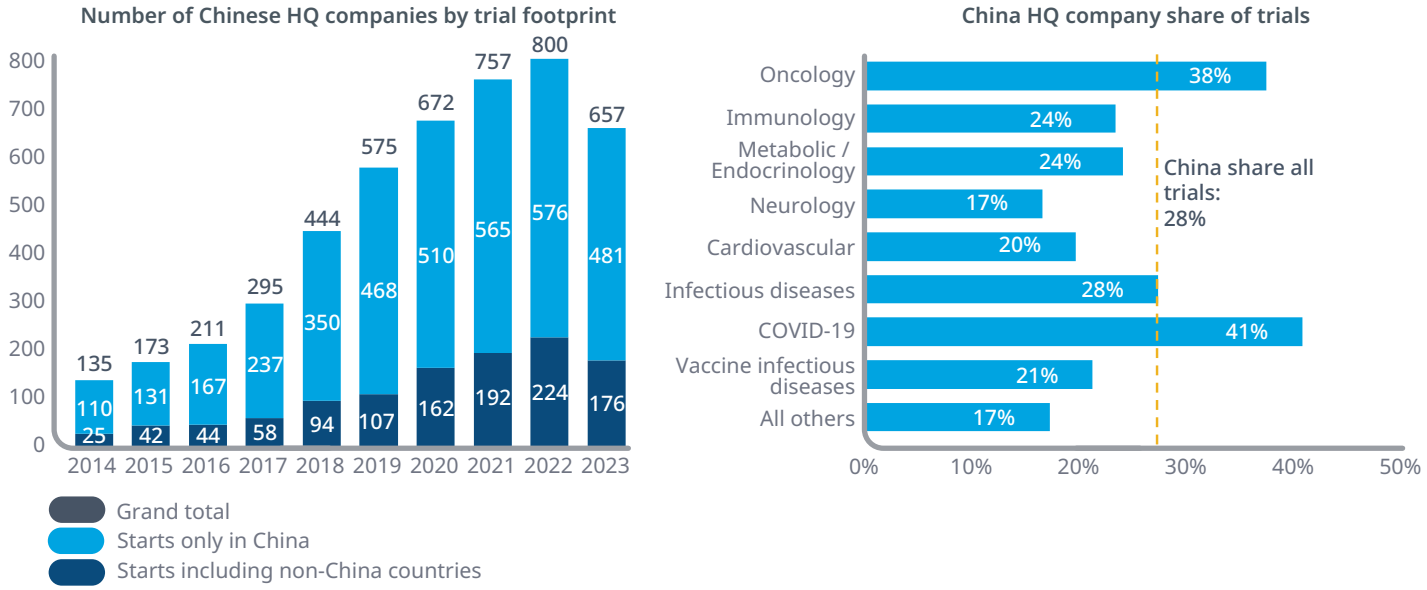
Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Jan 2024.

- Trial starts are sponsored by companies from across major geographies, with 2,357 companies sponsoring trial starts in 2023, up from 993 in 2008 and reflecting a halving in the average number of trials per company — from four in 2008 to two in 2023 (data not shown).
- The rising participation of companies headquartered in China is the most dramatic change over the period, with their share of starts rising to 28% from 3% in 2013 and 1% in 2008.
- The share of starts from companies headquartered in Europe has declined from 38% in 2013 to 23% in 2023, and these companies now start about two-thirds as many trials as U.S. headquartered companies, whereas in 2013 and earlier years, European HQ companies started more trials than U.S. companies.
- Japanese companies' share of trial starts has declined to 4% from 11% in 2013 and are consistent with the decline in starts from 501 to 244 over the same period.
- South Korea is home to a dynamic group of companies including generics and biosimilars, and as their share of trial starts has risen, it reflects the increasing importance of the multiple niches these companies occupy.

Notes: Includes interventional, industry sponsored trials which are in Phase I to Phase III. Each company involved in a trial is counted individually, so products with more than one company involved are counted more than once and trials may be included in more than one region to reflect their sponsors headquarter geography. Europe is defined as any country in continental Europe. Trial sponsors are subject to variations in company naming and industry consolidation may result in multiple companies being counted individually when they are part of a larger corporate parent.

Over one quarter of Chinese companies are active internationally; Chinese firms are focused on oncology and COVID-19

Exhibit 12: Industry interventional trials Phase I to III



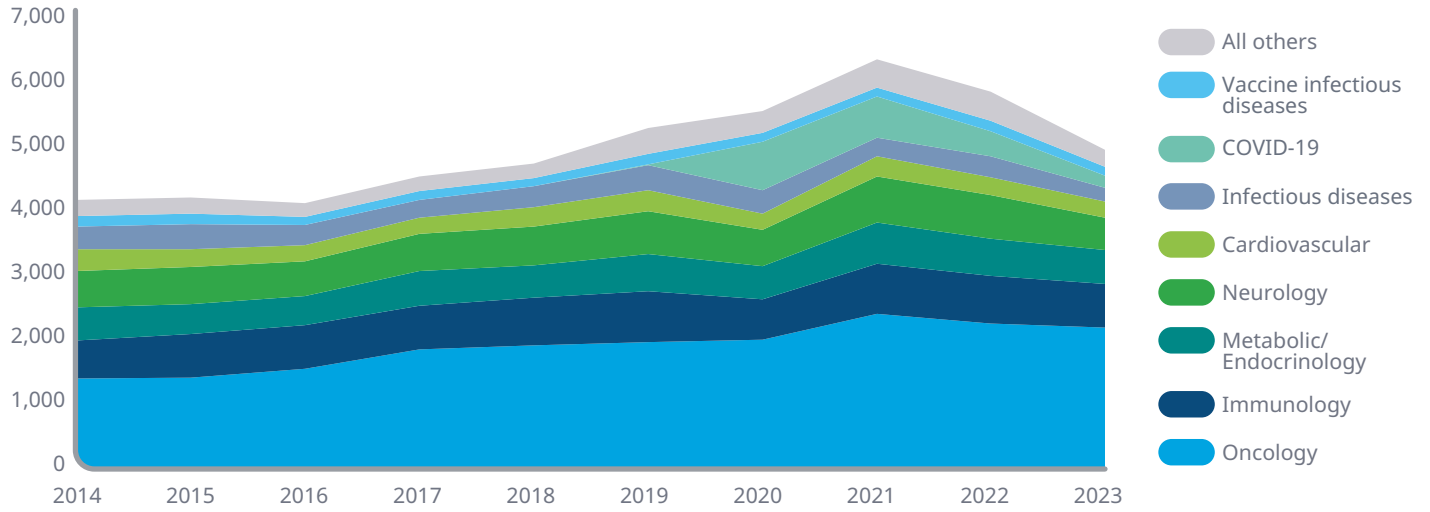
Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Jan 2024.

- For industry interventional trials, sponsors with a Chinese headquarters started 657 trials in 2023, down from 800 in 2022, but a consistently high number indicates the growing activity of these companies.
- Most Chinese companies have only had trial starts with sites in China, while 27% of the companies have included non-China sites in trials they're involved with (which may include non-Chinese partners).
- Domestic-only companies have between one and two trial starts per company per year, whereas those companies with some international activity have averaged four to five trials per company, suggesting this international aspect is related to the growth and maturation of these firms.
- Chinese companies have a greater focus on earlier phases in their trials than the industry overall, as trials with sites in China are a leading location for these early phase studies globally (Exhibits 42, 52).
- China HQ companies accounted for 28% of trial starts in 2023 (Exhibit 11) but have a higher percentage of trial starts in oncology and COVID-19, illustrating the relatively higher focus those diseases have in these companies' priorities.

Notes: Includes interventional, industry sponsored trials which are in Phase I to Phase III. Chinese headquartered companies have been analyzed for the countries included in trials they started each year, and the company has been assigned to a segment based on whether those trials included international countries in any of the trials they started. Not all of a company's trials are China-only or including non-China sties. Disease and therapy areas for trials are mutually exclusive.

The top 4 diseases account for 79% of trial starts and declined less than other diseases

Exhibit 13: Clinical trial starts by therapeutic area, Phases I to III, 2014–2023



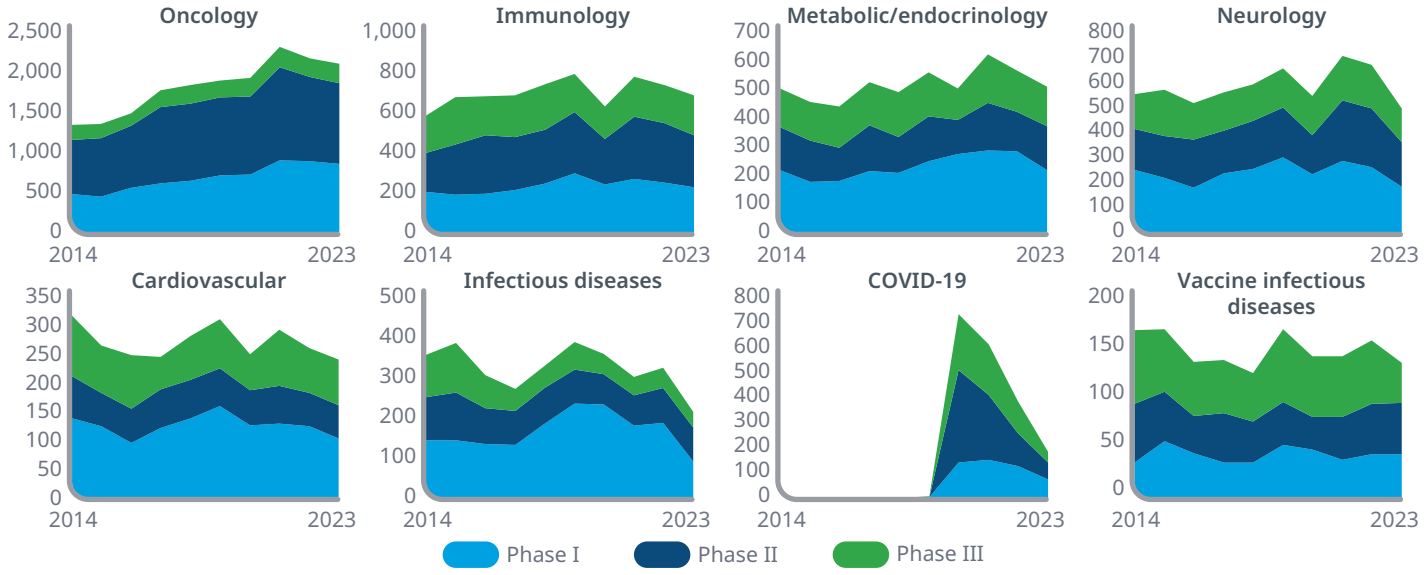
Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Jan 2024.

- Trial starts declined 15% in 2023 with 4,873 trials started or planned to be started from Phase I to Phase III, reflecting a 52% reduction in COVID-19 trial starts since 2022 and slower declines in all other therapy areas.
- Oncology remains the focus of the pipeline, comprising 44% or 2,143 trials and down 3% since 2022.
- Immunology trials accounted for 14% of starts in 2023 and were down 7%.
- Neurology represented 10% of trials, down 26% in 2023 and including a mix of rare diseases as well as larger population research targets.
- Cardiovascular trials were 5% of trial activity and down 7% in 2023, slowing less than all therapies except oncology and immunology.
- Vaccines for infectious diseases saw 131 trial starts, down 14%, and infectious disease research excluding vaccines or COVID-19 declined 34% in the past year, potentially resulting from above normal starts in prior years.

Notes: Includes drugs with an active research program, with phase determined by the highest phase of research regardless of indication. Includes industry sponsored, interventional trials. Endocrinology includes diabetes, other endocrinology and GI/NASH. All others includes (women's health, other genitourinary excluding women's health, respiratory, hematology, and all others). Immunology includes autoimmune and inflammation. Oncology includes both solid-oncology and hematology oncology. Neurology is mental health and other CNS. Vaccines are infectious disease vaccines (i.e., cancer vaccines are not included). Infectious diseases are not including vaccines or COVID-19. COVID-19 include any trials which mention COVID-19 and could include repurposing of existing therapeutics.

Clinical trial starts in key disease areas slowed with variations by phase, highlighting differing maturity of research pipelines

Exhibit 14: Clinical trial starts by year and phase, 2014–2023



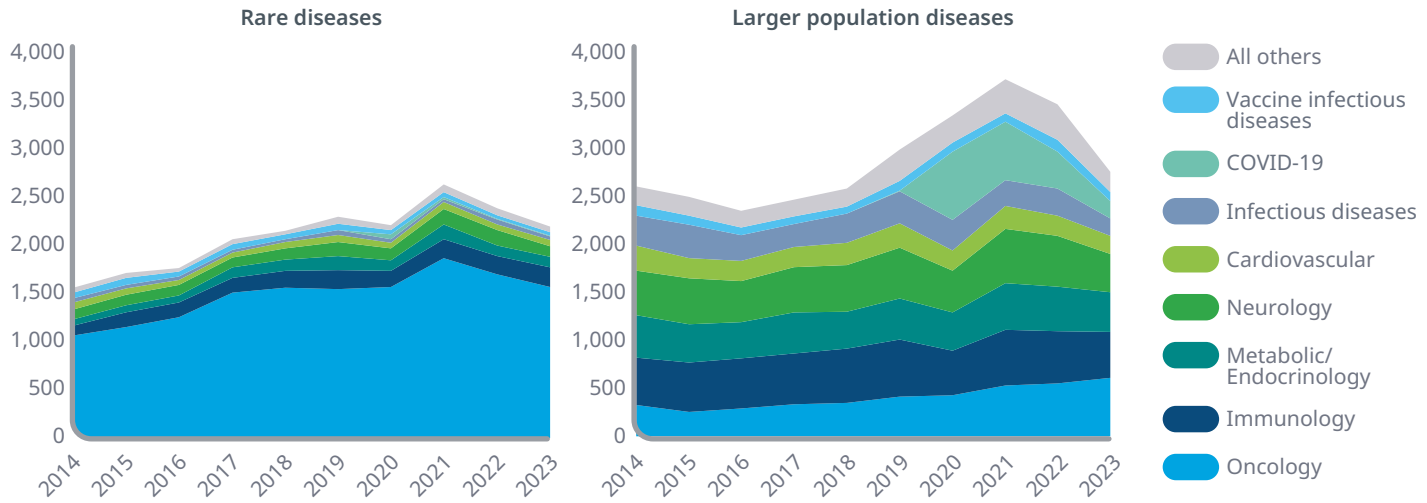
Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Jan 2024.

- The top four disease areas for trial starts — oncology, immunology, metabolic/endocrinology, and neurology — combined accounted for 79% of trial starts but declined by 8% compared to the overall market, which had 15% fewer starts in 2023.
- The smallest declines overall were in oncology (3%), immunology (7%), and cardiovascular (7%) in 2023 compared to 2022, with trial starts exceeding 2020 levels in oncology, immunology and metabolic/endocrinology.
- COVID-19 starts dropped by 52% in 2023, bringing the starts to just one quarter of the number of starts in 2020 at the peak of early pandemic research.
- Across therapy areas, the declines have been more concentrated in Phase I and Phase II clinical trials, except for infectious diseases (including COVID-19 and vaccines), where Phase III declines were greater.
- While some therapy areas had a more pronounced interruption of trial starts in 2020 from COVID-19, most had recovered in 2021 and 2022 and all had declines in 2023.

Notes: Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Terminated trials are included to track the activity still involved with their initiation, partial execution and termination. Trials were industry sponsored, interventional trials and device trials were excluded.

Rare disease trial starts are focused in oncology while diseases with larger populations focus on a wider variety of diseases

Exhibit 15: Industry sponsored interventional trials by start date, Phase I to III, 2014–2023



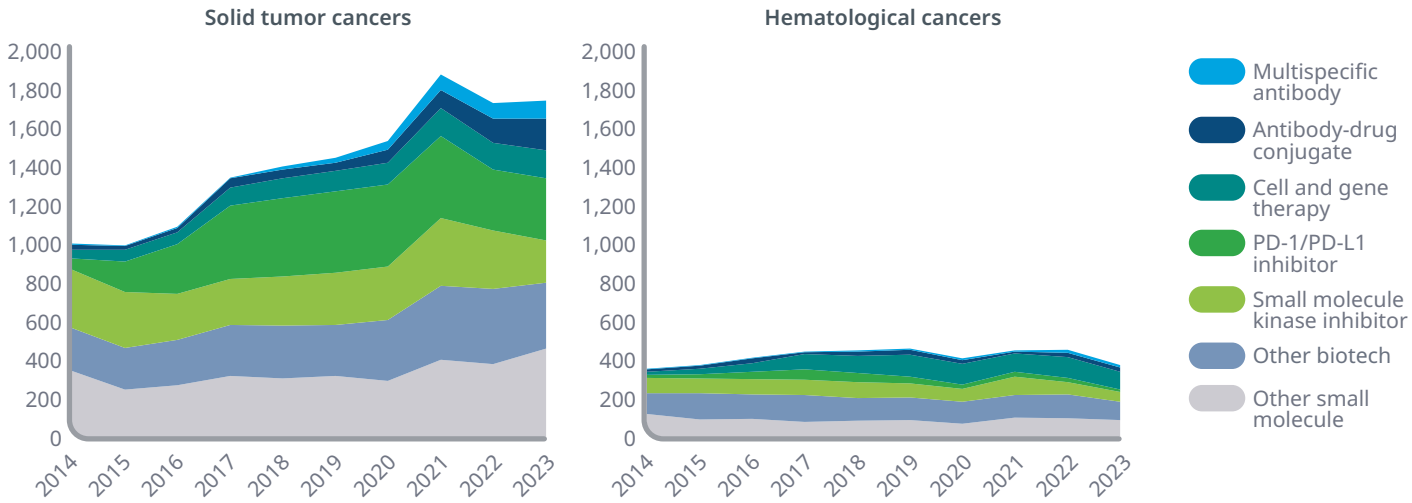
Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Jan 2024.

- Rare disease trials declined less (8%) than larger population trials (20%) in the past year.
- Oncology trials averaged 70% of rare disease trial initiations over the past decade; despite an 8% decline in 2023, the number of trials initiated remained above pre-pandemic levels and larger population oncology trials increased by 11% in 2023.
- Within rare diseases, immunology, cardiovascular, and vaccines starts increased in 2023 by 8%, 10% and 12%, respectively, compared to 2022, while other disease areas declined.
- In larger population diseases, all diseases except oncology had fewer starts in 2023, and all except vaccines had fewer starts than in 2020.
- Rare disease trials were 44% of trial starts in 2023 and an average 42% over the past decade, consistent with them having higher success rates than other research areas (Exhibit 38) and being 50% of U.S. NAS launches in the past five years (Exhibit 28).

Notes: Includes industry sponsored, interventional trials. Endocrinology includes diabetes, other endocrinology and GI/NASH. All others includes (women's health, other genitourinary excluding women's health, respiratory, hematology, and all others). Immunology includes autoimmune and inflammation. Oncology includes both solid-oncology and hematology oncology. Neurology is mental health and other CNS. Vaccines are infectious disease vaccines (i.e., cancer vaccines are not included). Infectious diseases are not including vaccines or COVID-19. COVID-19 include any trials which mention COVID-19 and could include repurposing of existing therapeutics.

Novel oncology mechanisms, especially cell and gene therapies, ADCs and multispecific antibodies have risen to 25% of trials

Exhibit 16: Oncology clinical trial starts Phase I to III, by primary tested drug type, 2014–2023



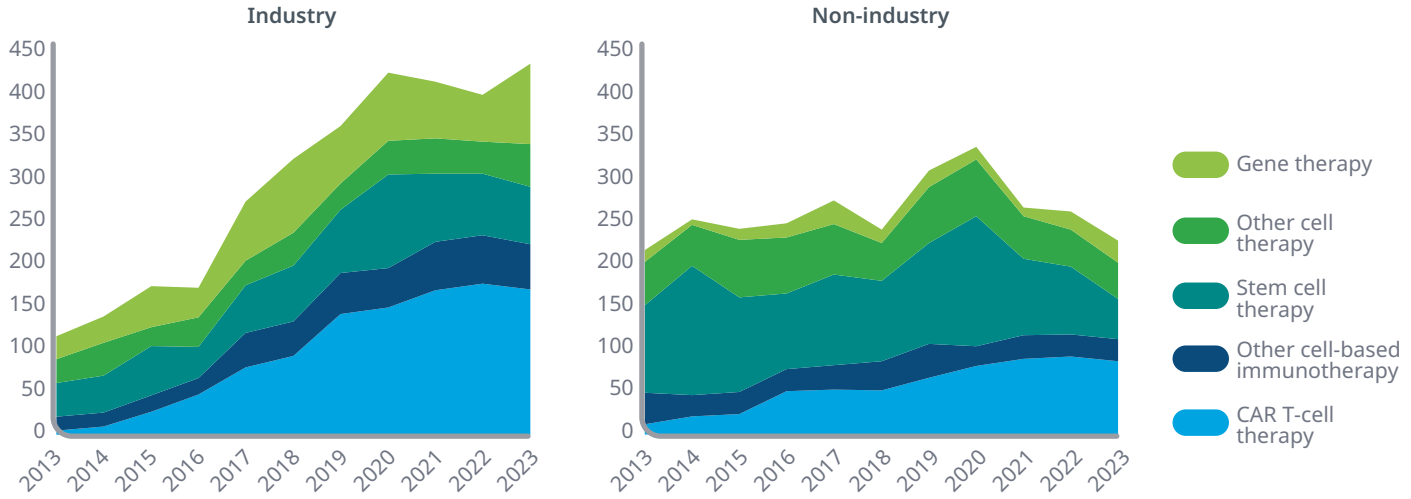
Source: Citeline Trialtrove, IQVIA Institute, Jan 2024.

- Oncology research and development has seen an increasing focus on targeted drugs with innovative mechanisms of action for treatment of cancers over the last decade.
- While development of drugs for hematological cancers declined 17% in 2023, clinical development for solid tumor cancers grew 1% when compared to 2022.
- Next-generation biotherapeutics are increasingly under investigation for hematological cancers, with trials started globally in 2023 more than five times what they were a decade ago and accounting for 25% of the hematological-oncology pipeline.
- PD-1/PD-L1 which saw significant growth over the last decade, is up by 2% in 2023 when compared with last year in solid cancers.
- Despite being first developed in the 1960s, multi-specific antibody development for cancer treatment was minimal a decade ago and has grown significantly, representing 5% of both the hematological-oncology and solid tumor pipelines, indicating an increasing focus on the ability of these molecules to act on multiple targets or through different mechanisms of action.
- Many new antibody-drug conjugates have been under development in oncology, representing 9% of the oncology pipeline in 2023 and allowing for targeting cytotoxic agents directly to cancer cells, improving on the non-specificity of older oncology products.

Notes: Trials are industry-sponsored, interventional trials phase I, II, and III. Trials are assigned a type based on disclosed information for the primary tested drug modality and mechanism. Segmentations are mutually exclusive.

Industry sponsored cell and gene therapy trials have more than tripled over the last decade while non-industry have grown 5%

Exhibit 17: Cell and gene therapy clinical trial starts by type, 2013–2023



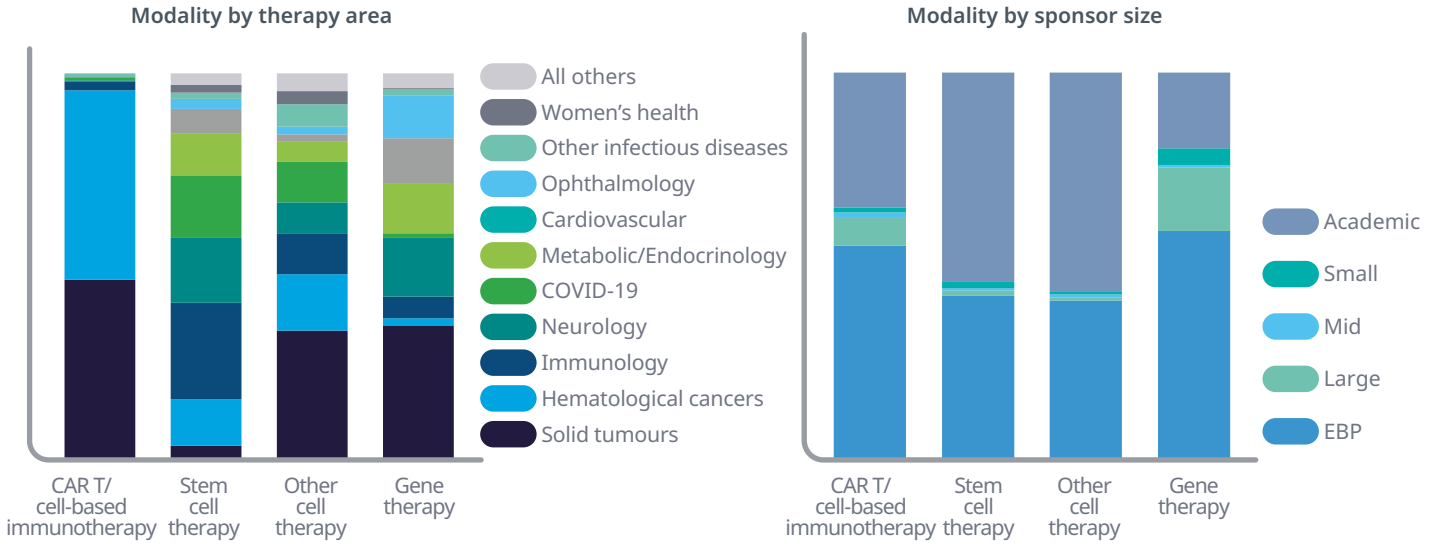
Source: Citeline Trialtrove, IQVIA Institute, Jan 2024.

- In 2023, 631 trials started for cell and gene therapies across all sponsor types; non-industry trials represented 36% of trial starts in 2023 with industry-sponsored trials (with or without non-industry involvement) accounting for the other 64%.
- While non-industry trials have remained relatively flat over the last decade, industry-sponsored trials are up 276% from 2013 and 34% from five years ago.
- Much of this increase can be attributed to the growing research of CAR T-cell therapies, up from just four industry-sponsored trials started in 2013 to more than 150 starts for the last three years.
- CAR T share of trials dropped in 2023 to 39% of cell and gene therapy trial starts from a peak of 44% in 2022 as gene therapy trials grew.
- Industry and non-industry sponsors have been focusing their research into different types of cell and gene therapies, but both have had a growing focus on CAR T-cell therapies, with 39% and 38% of industry and non-industry trials, respectively, started in 2023.
- The largest difference in research focus across industry and non-industry is in gene therapies, with 88 gene therapy trials (22%) started by industry in 2023 compared to just 26 (12%) by non-industry.
- Other cell-based immunotherapies such as natural killer (NK), T-cell receptor (TCR), and tumor-infiltrating lymphocyte (TIL) cell therapies account for 12% of all trials in 2023; stem cell therapies accounted for 38% of non-industry trials in 2019 but have dropped to 20% of their trials in 2023, similar to the share of industry trials (16% in 2023).

Notes: Includes Phase I, II, and III. Terminated trials are included to track the activity still involved with their initiation, partial execution and termination. Trials are interventional trials. Trials are categorized by type based on disclosed information. Other cell-based immunotherapies includes T-cell receptor, tumor-infiltrating lymphocyte, natural killer, and dendritic cell therapies. Non-industry trials include those sponsored by academic institutions, non-profits, and governments with no biopharma involvement.

CAR T-cell therapy clinical research is focused on oncology, while other diseases may benefit from other cell and gene modalities

Exhibit 18: Cell and gene therapy trial starts by therapy area and company size, 2019–2023



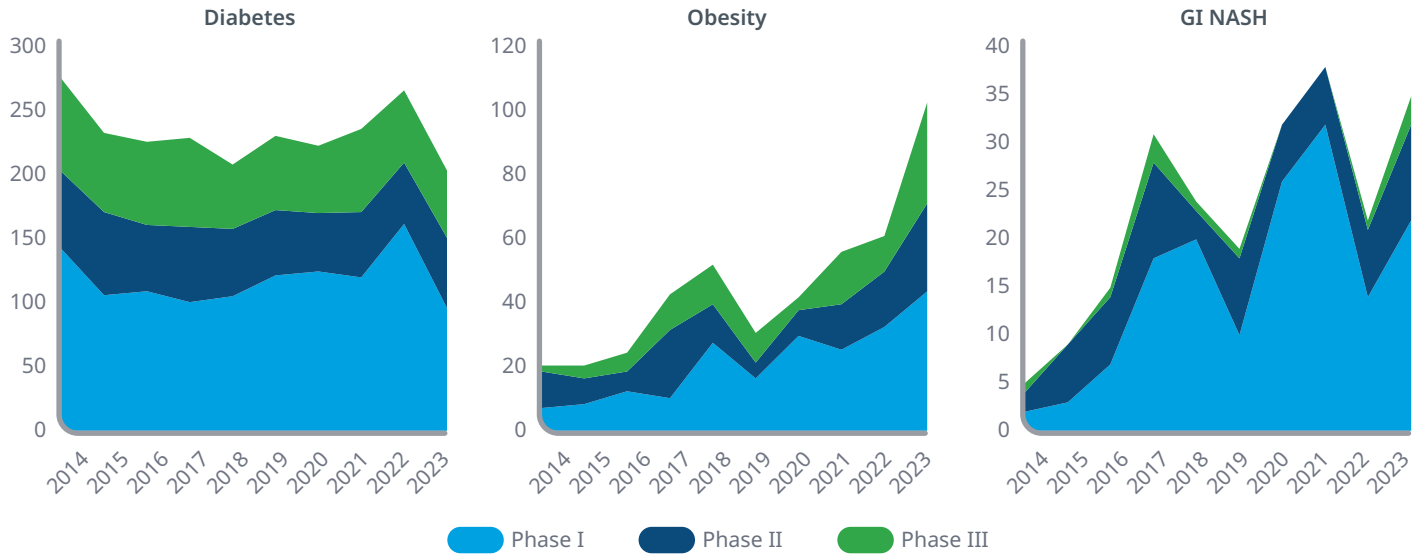
Source: Citeline Trialtrove, IQVIA Institute, Jan 2024.

- Cell and gene therapies are being investigated across a range of diseases and modalities and by different types of sponsors and companies; across cell and gene therapy modalities, more than 90% of trials are run by academic institutions and startups, highlighting the important role these groups play in scientific discoveries and developing novel treatment options.
- Cell-based immunotherapies, including CAR T, are overwhelmingly being investigated for treating cancer with success in hematological cancers including several CAR T-cell therapies available commercially and potential in solid tumors being investigated in trials.
- Immunology, neurology, and metabolic/endocrinology diseases account for 53% combined of stem cell therapy clinical trials.
- Gene therapies often focus on inherited diseases, providing promise for patients with lifelong or debilitating diseases, with one example of recent success the restoration of hearing in children across different studies in the U.S. and China with gene-mediated hearing loss.
- The size and type of the sponsor also varies by modality; emerging biopharma companies account for 55% and 59% of cell-based immunotherapy and gene therapy trial activity, respectively, but smaller shares in stem cell and other cell therapies, whereas larger pharma companies have little involvement in stem cell and other cell therapy research, but account for 10% of cell-based immunotherapy trials and 21% of gene therapy trials.

Notes: Includes Phase I, II, and III. Terminated trials are included to track the activity still involved with their initiation, partial execution and termination. Trials are interventional trials. Trials are categorized by type based on disclosed information. Company segment when two or more companies are involved is determined by the larger sales segment. Emerging biopharma companies (EBP) are those with either R&D spend less than $200Mn or global sales up to $500Mn per year. Small companies have global sales between $500 million and $5Bn per year; mid-sized companies between $5Bn and $10Bn per year; and large companies exceeding $10Bn per year.

Obesity clinical trials in 2023 were up by 68% from 2022, and nearly doubled when compared to 5 years ago

Exhibit 19: Industry sponsored interventional trials by start date, 2014–2023



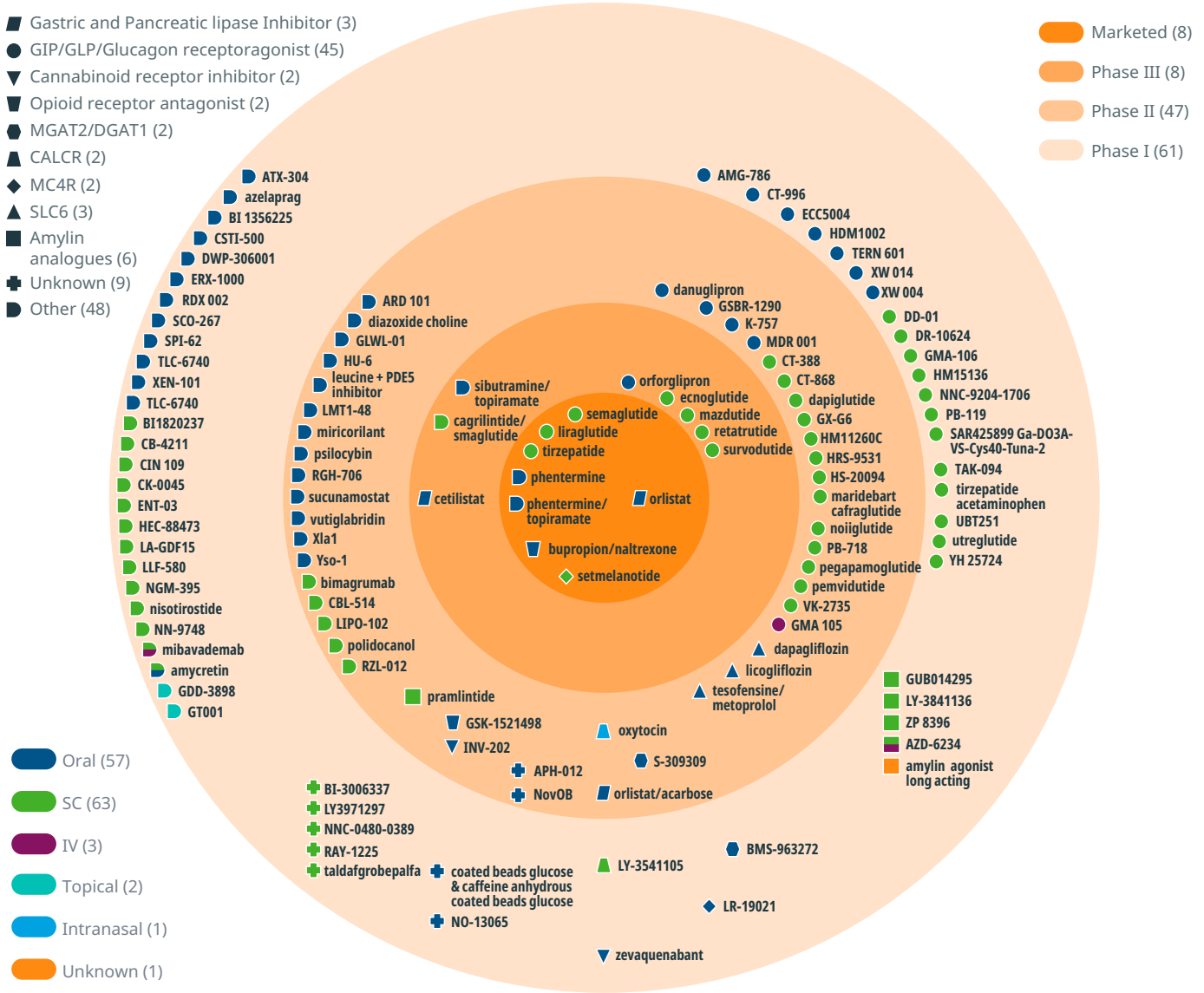
Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Jan 2024.

- Metabolic and endocrinology studies include trials in diabetes, obesity and for NASH, sometimes with the target medicines being investigated in more than one of these areas.
- Diabetes dominates the field of metabolic and endocrinology research, boasting a significant percentage of innovative contributions while comprising only 15% of non-novel substance in development in over the past five years.
- Trial activities around weight loss drugs have gained momentum in the recent years, with 68% increase in obesity trials start in 2023 compared to 2022 and nearly doubled over the past five years.
- Obesity pipeline focused majorly on GIP/GLP glucagon receptor agonists, representing 35% of the drugs in development.
- NASH is the most severe form of non-alcoholic fatty liver disease (NAFLD), characterized by the accumulation of excessive fat deposits in the liver, where the role of insulin resistance in fat accumulation may be related to sponsors investigating diabetes drugs for NASH; the enduringly high unmet need in NASH has drawn growing interest from major pharmaceutical companies.[3]
- Driven by significant attention from the biopharmaceutical sector in R&D investment, the NASH trials initiation has witnessed an 84% growth in 2023 compared to 2019, with majority of assets in early-stage of clinical development.

Notes: Trials may be included in more than one segment. GI NASH refers to a cluster of diagnoses related to Non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH).

With 124 drugs in development, over 35% drugs are GIP/GLP glucagon receptor agonists and 46% are orals

Exhibit 20: Obesity pipeline by phase, target and route of administration



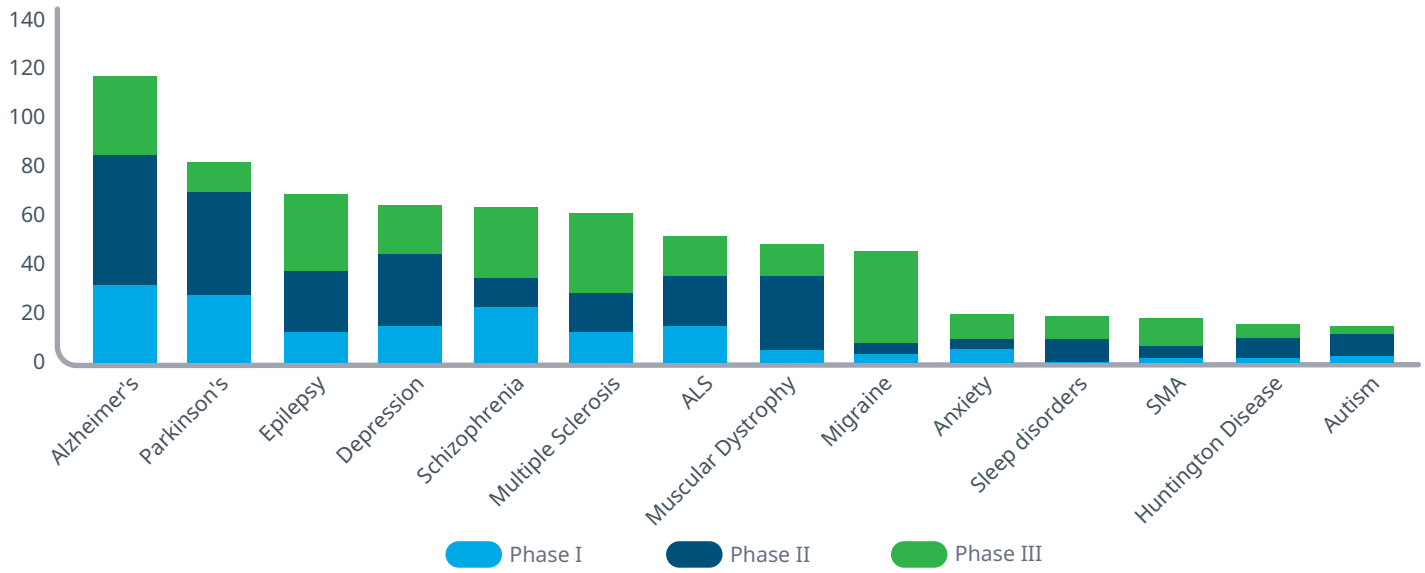
Source: Citeline Trialtrove, IQVIA Institute, Jan 2024.

- Obesity is a major public health threat globally; the rates for the disease have been increasing steadily over the last three decades and is likely to affect 1 billion adults by 2025.
- Of 124 drugs in development, eight are marketed and the remaining majority (55%) are in Phase I of development.
- The pipeline is dominated by the presence of GIP/GLP Glucagon receptor agonists (45), which have gained popularity in the segment with the approval of semaglutide (Wegovy) in 2021.
- Of the total drugs, 50% of development is happening in the subcutaneous segment and 46% in oral, promising greater convenience.

Notes: Only the highest phase details of an asset are considered for creating the chart. *semaglutide is also being developed in Oral setting by Novo Nordisk. The same scenario can be with others.

Neurology research is focused on Alzheimer's, Parkinson's and epilepsy, with a range of other often rare diseases

Exhibit 21: Active trials in neurology Phase I to III by disease type, 2019–2023



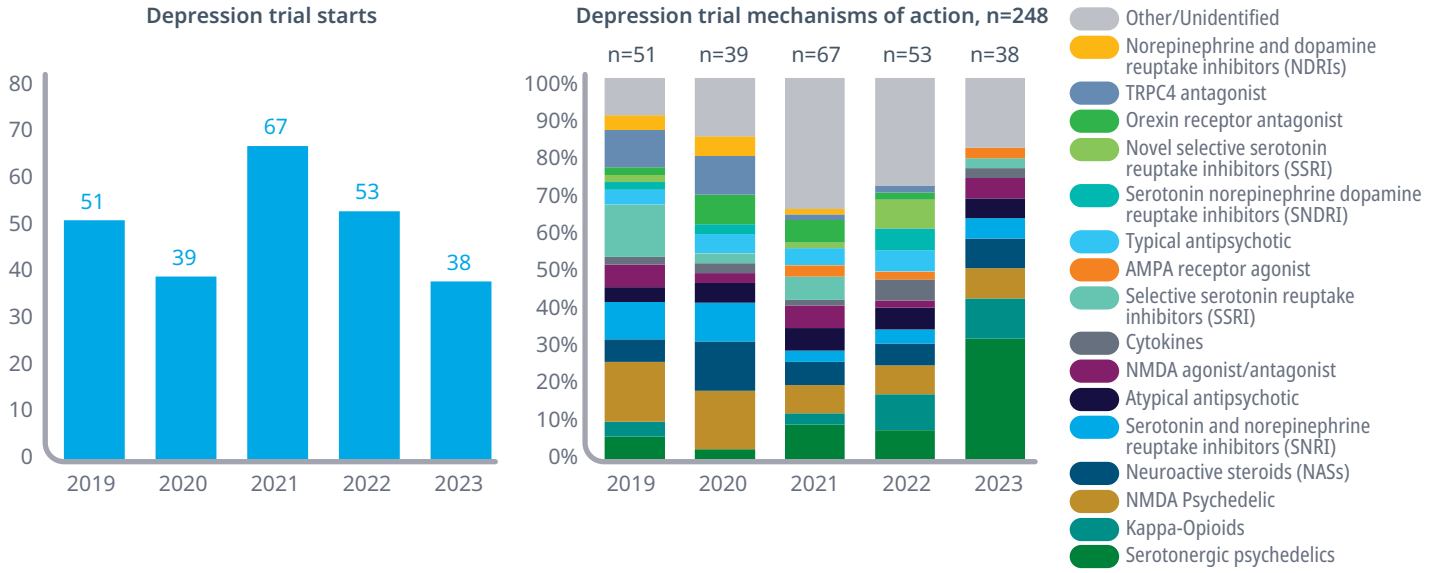
Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Jan 2024.

- Neurology has significant growth with more than 500 trials globally over the last five years, including products to treat neurodegenerative, neuromuscular, and psychiatric disorders.
- Much of the ongoing research is focused on Alzheimer's and Parkinson's diseases, with 117 and 82 trials globally, respectively.
- In 2023, FDA approved omaveloxolone (Skyclarys), the first drug to treat Friedreich's ataxia, a rare neuromuscular disorder that leads to loss of coordination, muscle weakness, fatigue.
- Currently marketed products for Alzheimer's disease are focused on symptom management, with recent exceptions including aducanumab and lecanemab; however, most of the products under clinical development are disease modifying.
- Depression and other mental health conditions have become more prevalent and recognized, particularly during the pandemic, and account for an increasing amount of the neurology pipeline, with ongoing trials globally — 65 for depression, 20 for anxiety.
- Other rare neurological diseases, such as amyotrophic lateral sclerosis (ALS) and Duchenne muscular dystrophy, continue to receive attention in the pipeline, with promising therapies in development.
- In 2023, 88% of the neurology pipeline consisted of small molecule products, indicating their continued utility in a rapidly evolving space.
- Next-generation biotherapeutics, such as cell and gene therapies, are increasingly being investigated for neurologic conditions, comprising 5% of the pipeline over last five years.

Notes: Analysis includes trials started 2019-2023 with open, closed and temporary closed. Trials for more than one indication may be included in more than one disease area. Other neurology diseases trials have been hidden in the graph.

Depression trial starts were 25% lower in 2023 than pre-pandemic with psychedelics being tested in nearly 40% of the 2023 trial starts

Exhibit 22: Depression clinical Phase I to III trials by segment and mechanism of action, 2019–2023



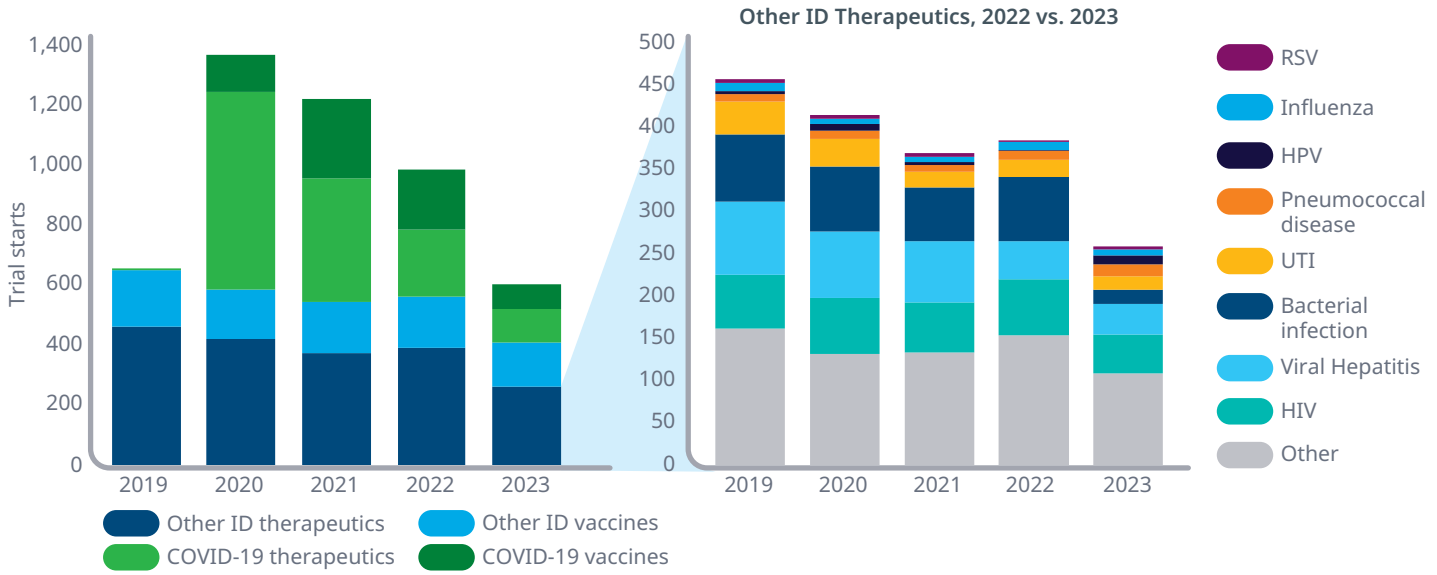
Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Jan 2024.

- Depression trials represent 9% of active neurology trials during the 2019-2023 period (Exhibit 21), where major depressive disorders remain the most active segment with 40% of 2023 trial starts (not shown).
- Since 2021, overall depression trial starts have decreased by 43% while the mix of mechanisms of action has shifted significantly.
- Activity around other key depression segments includes a focus in treatment resistant depression in more than 14% of trial starts and postpartum depression in 2% of trial starts in 2023 (not shown).
- Treatment-resistant depression research has ranged from exploring therapy treatments using ketamine (a psychedelic) and deep brain simulation (DBS) to the recent discovery of a biomarker used as a measure indicator for treatment resistant depression disease recovery.[4]
- There are a variety of emerging novel mechanisms becoming a focus, including serotonergic psychedelics, kappa-opioids, NMDA psychedelics and neuroactive steroids, which together account for just under 58% of the 2023 trial pipeline.
- Despite psychedelics representing just over 15% of the trial starts last year, their uptake increased by 24% of the trial starts in 2023. Recent breakthroughs have identified non-hallucinogenetic psychedelic treatment potential in serotogenic psychedelics, which alone account for almost 32% of the active trials in 2023.[5]

Notes: Trials may focus on more than one segment and depression segment analysis includes some double counting as a result. Trials could be included in other disease segments throughout the report. Trials are for CNS: Depression and CNS: Bipolar, include only Phase 1-3 trials, and non-bioequivalence (generic).

Infectious disease trials slowed to below pre-pandemic levels from both COVID-19 trials and other infection targets

Exhibit 23: Infectious disease clinical trial starts by disease, 2019–2023



Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Jan 2024.

- New COVID-19 trials have dropped to less than 75% the level in 2020 as fewer new targets have been identified.
- Overall, non-COVID-19 infectious disease trial activity has focused on therapeutics to a greater degree than vaccines.
- Infectious disease trials show a dip in non-COVID-19 starts in early 2020, concurrent with the appearance of the first COVID-19 trials, but by mid-2020 had rebounded, nearly tripling those of infectious disease trial starts.
- In the past five years, the ID therapeutics segment has seen a decrease in the number of trials; however, there has been an increase in the relative percentage of trial initiations for HIV, pneumococcal disease, HPV, influenza, and RSV.
- Conversely, the relative activity share in the bacterial infections segments has seen a decline, accounting for just 6% of the share in 2023; this trend underscores the ongoing deficiency of novel mechanisms and targets as well as the escalating risks associated with antimicrobial resistance.

Notes: Industry Sponsored Interventional Trials, terminated trials included in the analysis. Other ID therapeutics and vaccines exclude COVID trials.

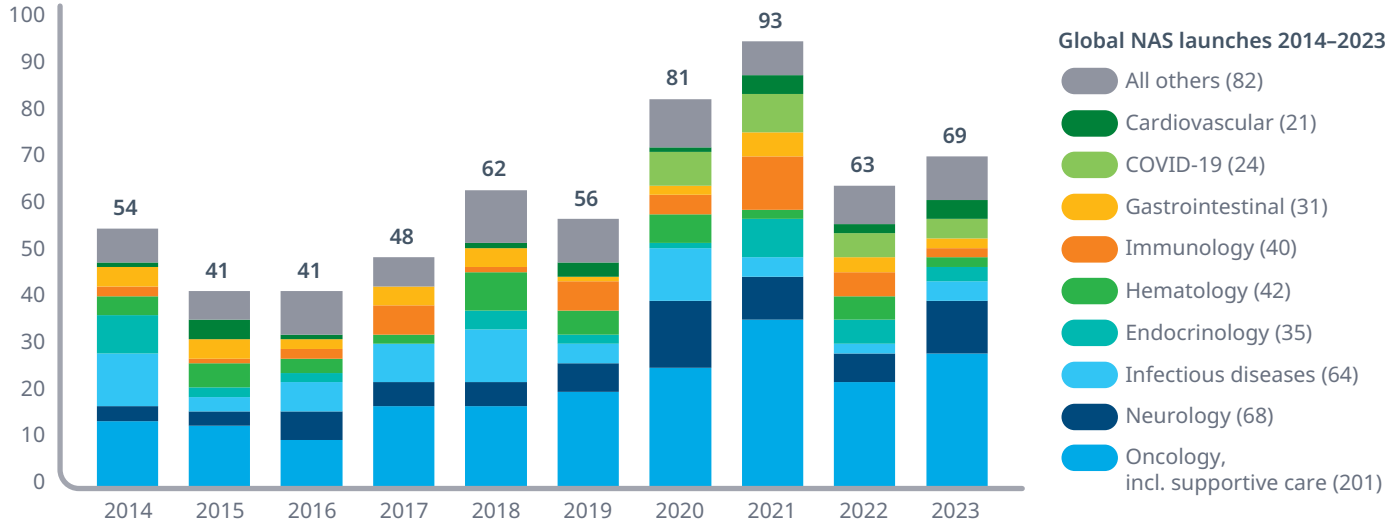
New drug approvals and launches

- A total of 69 novel active substances (NASs) were launched globally in 2023, up six from the prior year and representing a return to pre-COVID-19 trends of NAS launches.
- A total of 362 novel active substances have launched globally in the past five years, bringing the 20-year total to 942 and highlighting an increasing gap between countries such as the U.S., with 267 NAS launches, and the EU4+UK, with 182, and China, which becomes the second largest with 192.
- While the number of NAS launches in China is rising, an increasing number are not available in other countries, reflecting both a rising domestic industry and a mix of reduced barriers and increasing incentives for multinational NAS launches.
- Global NAS launches excluding China-only NASs were up one to 52 in 2023; global launches averaged 60 per year in the past five years compared to 48 per year during 2014–2018.
- There is a growing gap between the drugs launched in the U.S. and those available to patients in the largest European countries, with 113 drugs (42%) launched in the U.S. in the past five years that are not available in Europe, versus only 11 or 6% of European launches not available in the U.S.
- First-in-class NAS launches continue to emerge from research, including six first-in-class cell and gene therapies launched in 2023, along with firsts in menopause, neurology and oncology.
- Emerging biopharma companies originated 56% of all new drugs in 2023 and launched 53% of them, less than in recent years but still more than in the first half of the decade.

Launches of novel medicines reach countries around the world at different times and while there have been hundreds of new drugs, many with significant clinical benefits, patients across countries don't have access to all of them.

A total of 69 novel active substances (NASs) were launched globally in 2023

Exhibit 24: Global launches of novel active substances (NAS) by therapy area, 2014–2023



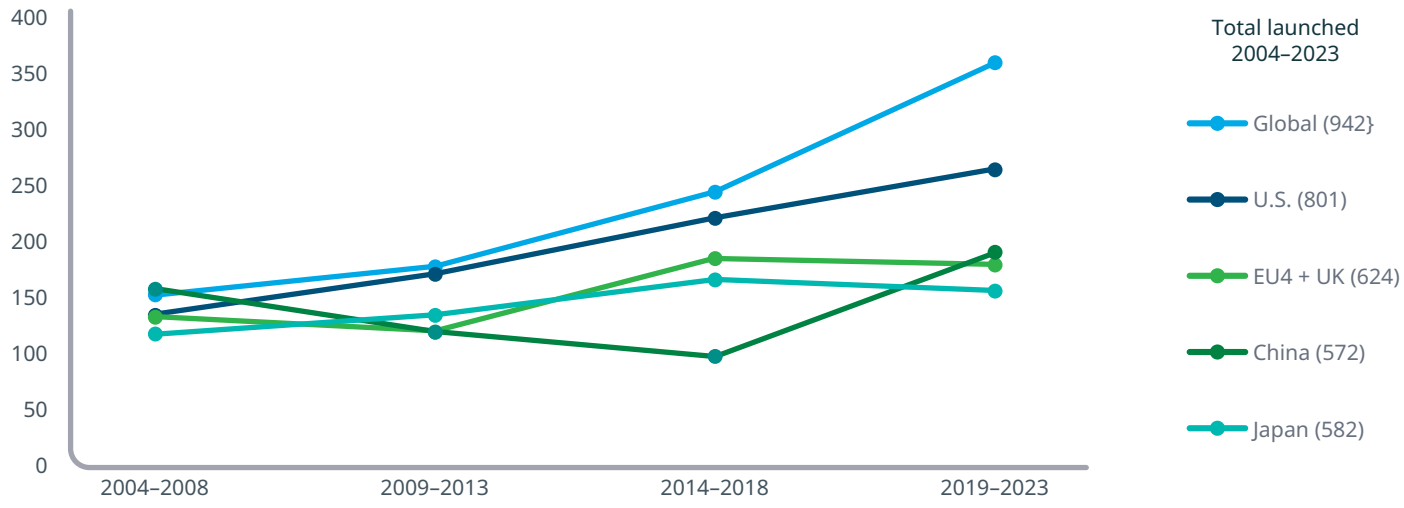
Source: IQVIA Institute, Jan 2024.

- A total 69 novel active substances (NASs) launched globally in 2023, indicating a rise of 10% from 2022 additionally representing a return to pre-COVID-19 levels.
- Oncology, neurology, and immunology have had rising shares of new launches in the past five years, with 204 of the 362 launches (56%) compared to 105 of 246 (43%) from 2014 to 2018.
- Infectious diseases, including anti-bacterial, anti-viral, anti-fungal and anti-parasitic treatments, have included novel treatments for HIV, Ebola, and more recently smallpox, and are 11% of NAS launches over the last decade, with some year-to-year variability.
- NAS launches for COVID-19 have gone down from seven launches in 2020 to four launches in 2023. Of which three launches are only in China and one in the U.S.
- The total 201 oncology launches in the past decade include cell and gene therapies (11), as well as innovative modalities like antibody-drug conjugates (12) and bispecific antibodies (9).
- Neurology includes 68 drugs launches in 10 years, of which the recent launches in 2023 are for rare diseases including Pompe disease, Friedreich ataxia, Rett syndrome and Duchenne muscular dystrophy.

Notes: A novel active substance (NAS) is a new molecular or biologic entity or combination where at least one element is new. Includes NASs launched anywhere in the world by year of first global launch. Launch is determined using IQVIA audits of sales activity as well as companies' public statements. Oncology includes supportive care & diagnostics. COVID-19 includes novel medicines only, and does not include previously approved medicines with new approved uses for COVID-19.

A total of 362 novel active substances have launched globally in the past 5 years, bringing the 20-year total to 942

Exhibit 25: Number of novel active substances (NASs) launched globally and in selected countries, 2004–2023



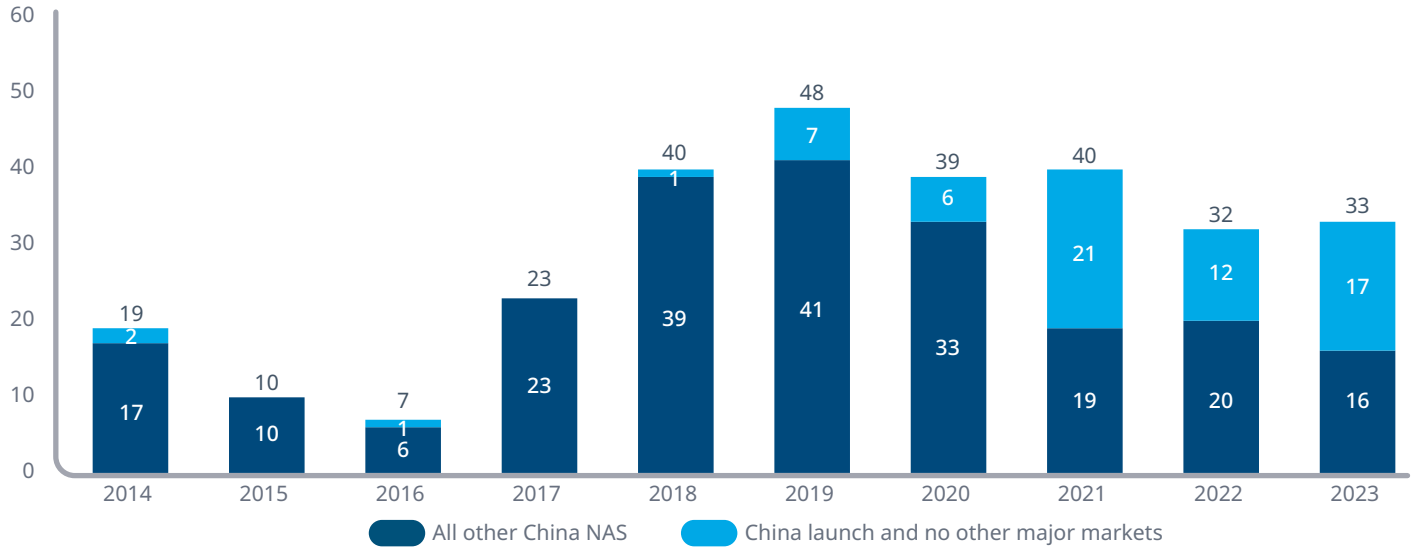
Source: IQVIA Institute, Jan 2024.

- A total of 69 novel active substances have launched for the first time globally in 2023, bringing the five-year total to 362. Based on molecules in the late-stage pipeline, over the next five years an average of 65–75 NASs are expected to launch annually, expanding the number of NASs launched globally by 325-375.[6]
- U.S. launches totaled 57 in 2023, marking a 50% increase in the number of launches within a single year compared to the last year. This surge in activity has contributed to a five-year total of 267 launches.
- With 33 confirmed NAS launches, China's total for the past five years stands at 192. This is a significant increase compared to the 99 launches from 2014–2018. As a result, China ranks second in the number of launches over the last five years.
- The four largest EU member countries (France, Germany, Italy, Spain) and the UK saw 22 launches in 2023, the lowest since 2014, totaling 182 in the last five years and representing a widening gap to U.S. and global NAS launches.
- Japan had 20 NAS launches in 2023, the lowest since 2014, and although launching sooner after global launch than earlier in the century, the country remains behind the U.S. and other major markets.

Notes: Novel active substance (NAS) is defined as a medicine with at least one novel ingredient and is noted in the year it launches for the first time in the relevant geography. Fixed-dose combinations are NAS if one of the ingredients is novel, but would not be considered NAS if both are previously available alone or in other combinations. Emergency use authorizations (EUA) are counted as NAS in the year the medicine became available to patients and no exclusion is applied for approval type. COVID-19 vaccines are counted as NAS based on which of the 8 subtypes of vaccine technology was used to create them. Launch of NAS in each geography are counted independently, meaning the totals for each geography include different products, and the global is a representation of distinct first global launches.

NAS launches in China in the past decade totaled 291, with 67 not yet launched elsewhere

Exhibit 26: NAS launches in China compared to other countries, 2014–2023



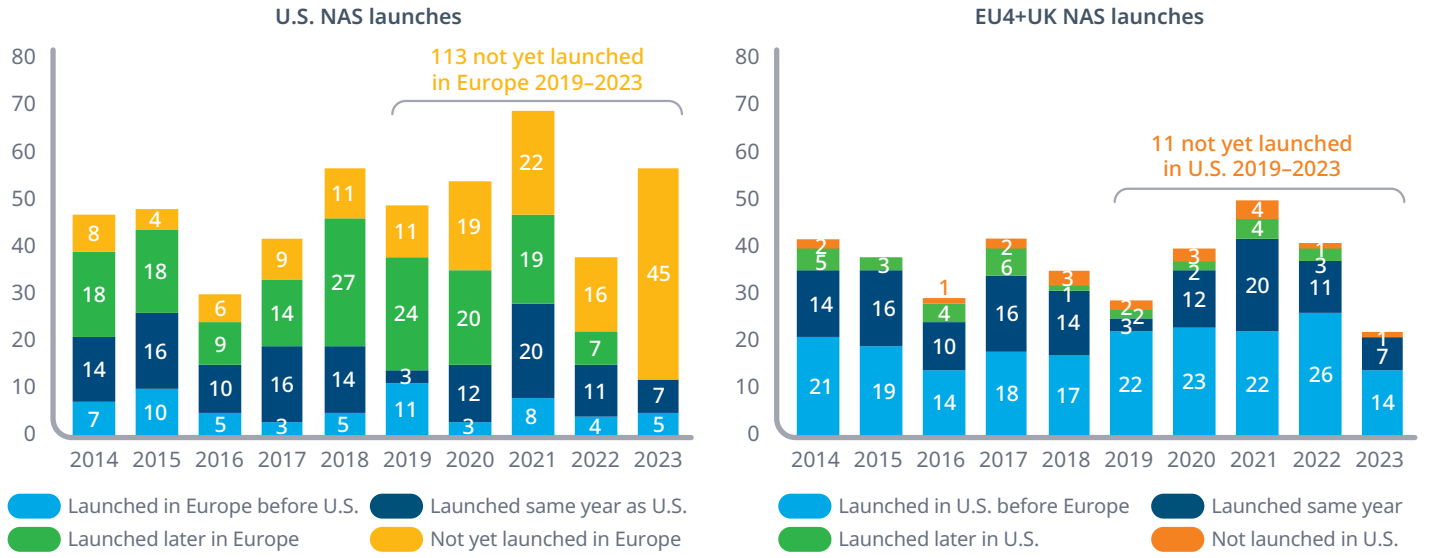
Source: IQVIA Institute, Jan 2024.

- There have been more than 30 NAS launches in China for a sixth consecutive year, making the five-year total now second after the United States in global launches, passing the four largest European countries and the United Kingdom.
- Updates to the national reimbursement drug list (NRDL), which shifted to annual frequency in 2019, were a factor encouraging multinationals to launch in the country, with a backlog of global launches reaching the market in those years.
- More recently, most of the launches were by domestic companies that have no other major market launches around the world, including 50 of the 105 in the past three years.
- The significant increase in NAS launches in China has begun to reduce the gap to other key geographies, bringing more novel medicines to China sooner.
- From 2014 to 2018, the United States' 224 NAS launches were 125 more than China's 99, whereas in the past five years, the U.S. had 267 launches — 75 more than China's 192.
- The key European markets (Germany, France, Spain, Italy and the UK) had 182 NAS launches in the past five years, 10 fewer than China.
- In the past five years, 129 of the NAS launches in China had also been launched in international markets at some earlier point, making that international total below the key European and Japanese markets (Exhibit 25).

Notes: NAS Launch dates reflect the availability of a medicine in the relevant geography regardless of reimbursement status. Launches tracked in U.S., EU4+UK, Japan and China. China launches by year assessed for launch of those medicines before (or since) in other major markets. Some China-only launches may eventually reach other geographies.

Since 2018, 113 U.S. NAS launches are not available in Europe, while 11 of Europe launches are not available in the U.S.

Exhibit 27: NAS launches in the U.S. and EU4+UK, 2014–2023



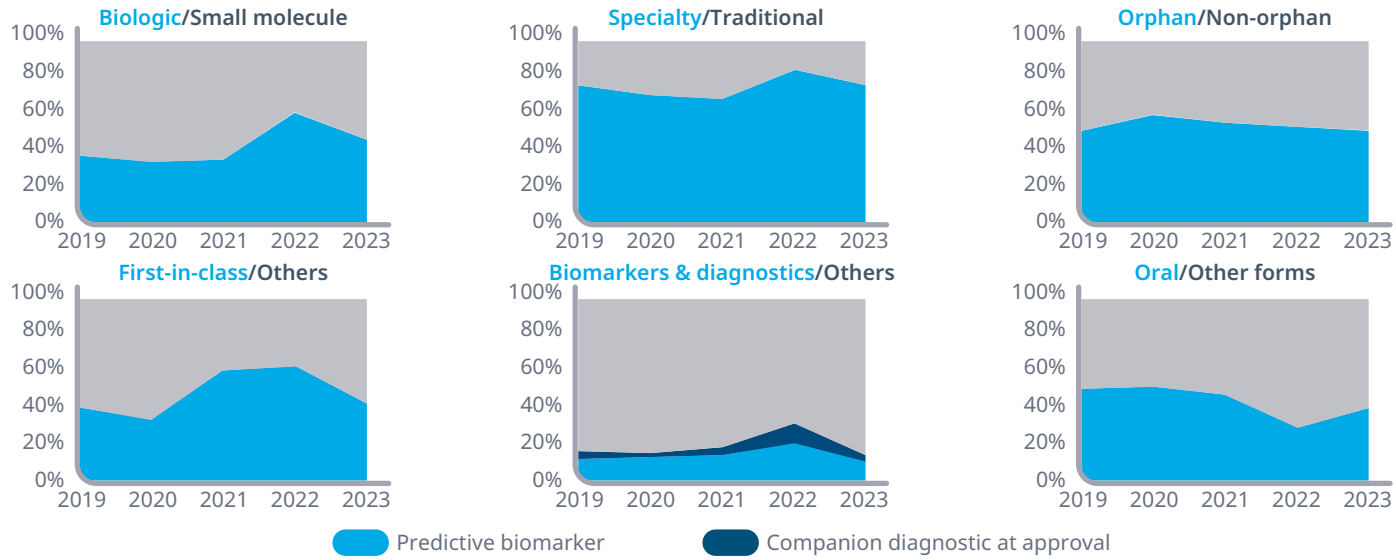
Source: IQVIA Institute, Jan 2024.

- Novel medicines do not launch in every country simultaneously, and increasingly there is a gap where medicines launched in the U.S. are not widely available in other countries.
- In the past five years there have been 113 (42%) U.S. NAS launches that have not yet been launched in the key European markets, while only 11 (6%) drugs launched in Europe have failed to be launched in the U.S.
- The U.S. is the most common first-launch country and there are often lags of a year or more to other country launches.
- These data mask these typical launch sequence patterns in the most recent two years, but older periods are indicative of more systemic patterns of incentives related to the relative commercial value of markets.
- In the five years from 2014 to 2018, there were 38 (17%) NAS launched in the U.S. that have not yet launched in Europe six to ten years later. In contrast, there are only eight (4%) drugs launched in Europe that have yet to launch in the U.S.

Notes: NAS launch dates reflect the availability of a medicine in the relevant geography regardless of reimbursement status. Launch dates in EU4+UK reflect the earliest of the five countries. U.S. NAS launches compared to their status in Europe. EU4+UK NAS launches compared to their status in the U.S. Information in most recent periods can be restated later and may change.

Over 40% of new launches in 2023 were first-in-class and about 50% were biologic, up from 35% 5 years ago

Exhibit 28: U.S. novel active substances (NASs) by product attributes and characteristics of clinical trials used for approval, 2019–2023



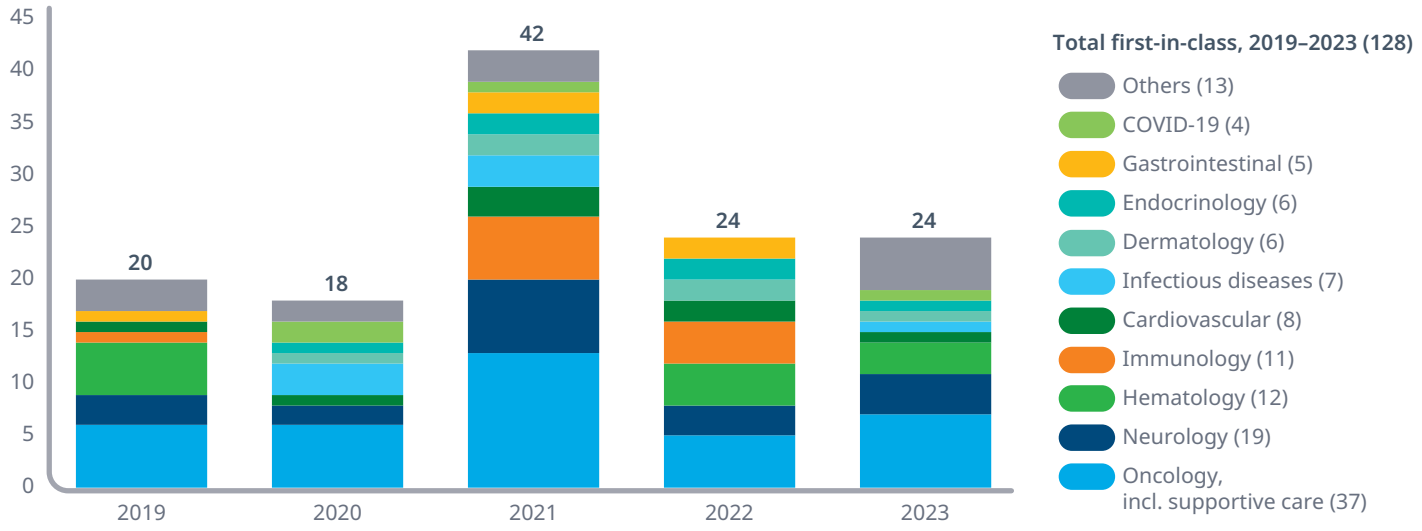
Source: IQVIA Institute, Jan 2024.

- A significant number of first-in-class medicines have become available, averaging 48% for the last five years, including 42% of those launched in 2023.
- Over the past five years, 144 drugs launched with orphan drug designations, representing 54% of the 267 launches, indicating a significant focus on innovative medicines for rare diseases.
- Specialty medicines — those which treat chronic, complex or rare diseases and which also have complex treatment, distribution or patient management aspects — along with often high costs, made up 75% of the launches in the U.S. in 2023. This proportion mirrors the levels observed in 2019.
- Of the 57 NASs launched in the U.S. in 2023, 46% were biologics. This represents a decrease in the proportion of biologic launches compared to 2022, which stood at 61%. However, this percentage is comparable to the figures from the three preceding years.
- While less than 20% of NASs include reference to a predictive biomarker or have a companion diagnostic in their approval, many more medicines have some degree of precision, with targeted mechanisms dominating key therapy areas such as oncology.

Notes: Includes NASs launched in the United States 2019–2023 regardless of the timing of FDA approval. Orphans include drugs with one or more orphan indications approved by the FDA at product launch. Products are not reclassified as orphan if they subsequently receive an approval for an orphan designated indication. First-in-class is based on FDA classification. Predictive biomarkers and companion diagnostics based on FDA approval information.

First-in-class NAS launches continue to emerge from research, including notable gene therapies in hematology and oncology

Exhibit 29: Therapy area share of first-in-class U.S. novel active substance (NASs), 2019–2023



Source: IQVIA Institute, Jan 2024.

- First in class molecules accounted for 42% of NAS launches in 2023 (Exhibit 28) and nearly half (48%) of the launches over the past five years.
- Keeping up with the trend in previous years, the majority (30%) of first in class molecules launched in 2023 were for oncology, followed by neurology (17%).
- In 2023, six first-in-class cell and gene therapies, including beremagene geperpavec (Vyjuvek), delandistrogene moxeparvove (Elevidys), donislecel (Lantidra), nadofaragene firadenovec (Adstiladrin), omidubicel (Omisirge) and valoctocogene roxaparvovec (Roctavian) were launched, indicating an increase of 50% compared to the launch of three such therapies in each of the two preceding years.
- Additionally, first RSV vaccine (Arexvy), a first direct hormone-free treatment fezolinetant (Veozah) for menopause, and first allogeneic pancreatic islet cellular therapy donislecel Lantidra for Type 1 diabetes were launched in 2023.

Notes: The details on the clinical benefit summary of these 2023 launched first-in-class molecules is given in exhibit 30 of the report. A novel active substance (NAS) is a new molecular or biologic entity or combination where at least one element is new; Includes NASs launched in the United States 2019–2023 regardless of the timing of FDA approval. First in class is based on FDA classification. Immunology/allergy name harmonized to Immunology.

Every first-in-class NAS launched in the U.S. in 2023 provides a distinct therapeutic solution for its specific target indications

Exhibit 30: First-in-class launched in 2023

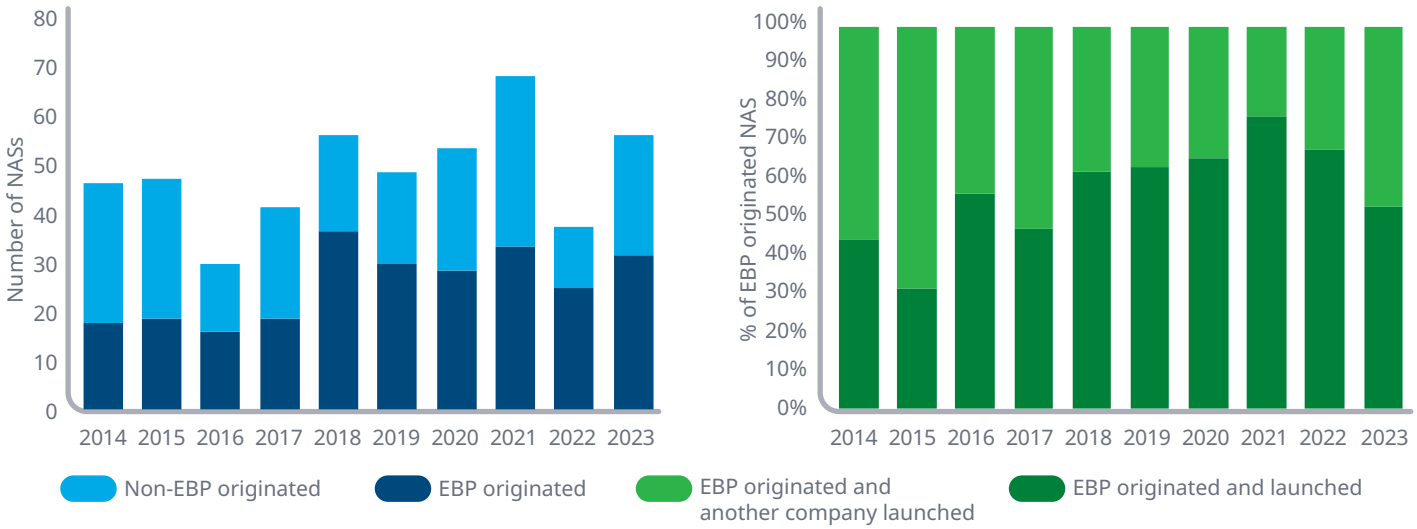
	FIRST-IN-CLASS NAS	INDICATION	MOA	CLINICAL BENEFIT SUMMARY
Cell & gene therapies	beremagene geperpavec (Vyjuvek))	Dystrophic epidermolysis bullosa	Transcription regulator	Vyjuvek reported higher efficacy of 65% complete wound closure compared to placebo group (26%) at 24 wks
	delandistrogene moxeparvove (Elevidys)	Duchenne muscular dystrophy	Dystrophin replacements; Gene transference	Patients treated with Elevidys reported NSAA score of 2.6 Vs 1.9 points placebo treated patients after 52 wks
	donislecel (Lantidra)	Type 1 diabetes	Pancreatic beta cell replacements	70% of patients met the composite efficacy end point were insulin independent at one year after transplant
	nadofaragene firadenovec-vncg (Adstiladrin)	Bladder cancer	Adenoviral vector-based gene therapy	51% achieved a complete response by 3 months out of which 46% remain free of high-grade recurrence at 12 months
	omidubicel (Omisirge)	Hematologic malignancies	Allogeneic hematopoietic stem cell therapy	Omisirge reported a median time to neutrophil recovery of 12 days (87% recovery) Vs 22 days (83% recovery) with standard cord blood
	tofersen (Qalsody)	Amyotrophic lateral sclerosis	Antisense oligonucleotide targets ALS-SOD1	Qalsody reduced CSF SOD1 protein, an indirect measure of target engagement by 35% Vs 2% in placebo group
	valoctocogene roxaparvovec (Roctavian)	Hemophilia A	AAV5 based gene therapy vector	Roctavian reported reduction in mean ABR with 0.5 bleeds/year for spontaneous bleeds and 0.6 bleeds/year for joint bleeds Vs SOC
Neuro & Women health	fezolinetant (Veozah)	Vasomotor symptoms in menopause	Blocks NKB signaling	Veozah significantly reduced frequency and severity of the Vasomotor symptoms compared to placebo starting at week 4
	omaveloxolone (Skyclarys)	Friedreich's ataxia	NF E2 related factor 2 stimulants	Skyclarys reported significant lower mFARS scores Vs placebo at 48 wks, with difference of -2.41 points and p-value of 0.0138.
	trofinetide (Daybue)	Rett syndrome	Analog of glypromate/glycine proline glutamate	Daybue reported significant improvement in MMRM analysis compared to placebo at 12 weeks
Bispecific Antibody	mosunetuzumab (Lunsumio)	R/R follicular lymphoma	CD20 x CD3 bispecific monoclonal antibody	Lunsumio reported ORR of 80% with mean duration of response of 2 years and Complete response was achieved in 60% of patients.
	talquetamab (Talvey)	Multiple myeloma	GPRC5D x CD3 Bispecific monoclonal Antibody	At lower dose of 0.4mg/kg, Talvey resulted in ORR of 73% and mean duration of response of 9.5 months
Other Oncology	capivasertib (Truqap)	Metastatic breast cancer	AKT inhibitor	Truqap in combination with Faslodex has reported to reduce disease progression or death by 50% Vs Faslodex alone
	nirogacestat (Ogsiveo)	Desmoid tumors	Gamma secretase inhibitor	Disease progression reduced by 70% with ORR – 41%, CRR-7% and median time of response of 5.6 months
	leniolisib (Joenja)	Activated PI3K-delta syndrome	Selective PI3Kδ inhibitor	Joenja reduced lymph node size by day 85 and increased naïve B cell count by 37% Vs Placebo
Infectious diseases	lenacapavir (Sunlenca)	Multi drug resistant HIV-1 infection	Capsid inhibitors	Sunlenca achieved an undetectable viral load (<50 copies/mL) at wk 52 and mean increase in CD4 count of 82 cells/μL
	vilobelimab (Gohibic)	COVID-19	Acts by blocking C5a receptor	Gohibic with SOC improved survival of invasive mechanically ventilated patients and lead to a significant decrease in mortality
All others	daprodustat (Jesduvroq)	Anemia due to chronic kidney disease	Stabilizes HIF-1α by inhibiting HIF-PH	Jesduvroq reported rapid increase in the hemoglobin level by 4.1% Vs 1.6% in patients treated with ESA in first 4 Weeks
	efanesoctocog alfa (Altuviiio)	Hemophilia A	Factor VIII replacements	Altuviiio reported significant bleed protection with a mean ABR of 0.70 (95% CI: 0.5-1.0) and a median ABR of 0.0
	lotilaner (Xdemvy)	Demodex blepharitis	GABA-A receptor antagonists	Xdemvy reported 68% of mite eradication (root cause of Demodex blepharitis) Vs 17% by placebo group
	palovarotene (Sohonos)	Fibrodysplasia ossificans progressiva	Retinoic acid receptor gamma agonist	Sohonos effectively reduced AHO volume by 54% with weighted linear mixed effect model vs no treatment beyond standard of care.
	perfluorohexyloctane (Miebo)	Dry eye disease	Lipid modulator	Miebo reported significant reduction in both tCFS score and VAS dryness score (-10.2) Vs Control saline group (-1.2)
	RSV vaccine (Arexvy)	Respiratory syncytial virus infection	Immunostimulant	Arexvy significantly reduce the risk of developing mild and severe RSV-associated LRTD by 82.6% and 94.1% respectively
	sparsentan (Filspari)	Reduction of proteinuria in IgA nephropathy	Blocks endothelin type A receptor & angiotensin II type 1 receptor	Filspari reported mean reduction of proteinuria from baseline of 49.8% for vs 15.1% for the active control group at 36 wks

Source: IQVIA Institute, Jan 2024.

Notes: Abbreviations: Wks: weeks, Yrs: years, SOD1-superoxide dismutase 1, AVV5: Adeno-associated virus serotype 5, NSAA: North star ambulatory assessment, ABR: Annual bleeding rate, SOC: Standard of care, CR: Complete response, ORR: Objective response rate, LSM: Least squares mean, ALS: Amyotrophic lateral sclerosis, R/R: Relapsed or refractory.

Emerging biopharma companies originated 56% of all new drugs in 2023 and launched 53% of them, less than in recent years

Exhibit 31: Companies originating and filing FDA regulatory submissions for NASs and percent of launches by NAS launch year, 2014–2023



Source: IQVIA Institute, Jan 2024.

- The number of novel active substances (NASs) originated by EBP companies that have launched has increased by 40% in the last five years, with 32 NASs launched in 2023 that originated from an EBP company.
- Although the share of NASs launched that are EBP-originated varies significantly from year-to-year, EBP companies have originated 57% of U.S. NAS launches over the past five years, up from 48% over the previous five years and indicating increased EBP innovation reaching the market.
- Products originated by EBPs are increasingly launched by an EBP company, indicating more independence on the part of EBP companies in taking products from innovation to market.
- EBP companies launched 53% of their own products in 2023, with 32 EBP originated and launched NASs. Although this figure is below the five-year average of 65%, it still exceeds the 50% mark, consistent with trends observed in previous years.

Notes: NAS launches in the U.S. have been segmented by the originator, which is based on the company which filed the first patent. The segmentation laid out in exhibit 1 is applied based on the revenue or R&D spend at the time of the patent filing. Launch company segmentation has been assessed by the FDA filing company, further verified by the status of that company in relation to acquisitions by other companies as often filing company does not change retroactively to reflect new ownership.

NAS launched in 2023 included 43 specialty drugs, 32 EBP-originated, 40 with expedited regulatory review and 29 orphan drugs

Exhibit 32: Novel active substances (NASs) launched in 2023 in the United States

***ATTRIBUTES KEY:** 1 = Oral, 2 = Biologic, 3 = Specialty, 4 = Next-gen biotherapeutic, 5 = Orphan, 6 = First-in-class, 7 = Expedited review, 8 = U.S Patent to launch ≤5 years 9 = EBP originated, 10 = EBP launched

THERAPY AREA	INDICATION	MOLECULE	BRAND	ATTRIBUTES*									
				1	2	3	4	5	6	7	8	9	10
Oncology, incl supportive care	Activated PI3K-delta syndrome (APDS)	leniolisib	Joenja	●		●		●	●	●			●
	Acute myeloid leukemia (AML)	quizartinib	Vanflyta	●		●		●		●			
	Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle-invasive bladder cancer (NMIBC)	nadofaragene firadenovec	Adstiladrin		●	●	●		●	●			
	Breast cancer	elacestrant	Orserdu	●		●				●			●
		capivasertib	Truqap	●		●			●	●		●	
	Cholangiocarcinoma	futibatinib	Lytgobi	●		●		●		●		●	●
	Desmoid tumors	nirogacestat	Ogsiveo	●		●		●	●	●			●
	Follicular lymphoma	mosunetuzumab	Lunsumio		●	●		●	●	●			
	Merkel cell carcinoma	retifanlimab	Zynyz		●	●		●		●		●	●
	Multiple myeloma	talquetamab	Talvey		●	●		●	●	●		●	
		elranatamab	Elrexfio		●	●		●		●			
		motixafortide	Aphexda			●		●					●
	Myelofibrosis with anemia	momelotinib	Ojjaara	●		●		●				●	
	Neutrophil recovery and infection with hematologic malignancies	omidubicel	Omisirge		●	●	●	●	●	●		●	●
	Prostate cancer	flotufolastat f 18	Posluma			●					●	●	●
	Refractory metastatic colorectal cancer	fruquintinib	Fruzaqla	●		●				●		●	
	Relapsed or refractory DLBCL	epcoritamab	Epkinly		●	●				●	●	●	●
	Relapsed or refractory large B-cell lymphomas	glofitamab	Columvi		●	●				●			
	Relapsed or refractory mantle cell lymphoma (MCL)	pirtobrutinib	Jaypirca	●		●		●		●		●	
	ROS1-positive Non-small cell lung cancer	repotrectinib	Augtyro	●		●		●		●		●	
Neurology	Alzheimer	lecanemab	Leqembi		●	●				●		●	
	Duchenne muscular dystrophy	delandistrogene moxeparvove	Elevidys		●	●	●	●	●	●			●
	Friedreich's ataxia	omaveloxolone	Skyclarys			●		●	●	●			●
	Generalized myasthenia gravis	rozanolixizumab	Rystiggo		●	●		●		●			
	Migraine	zavegepant	Zavzpret										
	Pompe disease (LOPD)	cipaglucosidase alfa	Pombiliti		●	●		●		●		●	●
	Postpartum depression	zuranolone	Zurzuvae	●						●		●	●
	Relapsing forms of multiple sclerosis (RMS)	ublituximab	Briumvi		●	●						●	●
	Rett Syndrome	trofinetide	Daybue	●		●		●	●	●		●	●
	Superoxide dismutase 1 (SOD1) gene mutated Amyotrophic lateral sclerosis	tofersen	Qalsody		●	●	●	●	●	●		●	

Source: IQVIA Institute, Jan 2024.

Table continued on the following page...

- There were 20 oncology NAS launches in 2023 — 13 with orphan designations and 7 first-in-class innovations.
- With oncology NAS launches, 17 of 20 received some form of expedited review and two progressed from first patent or first human trial to launch within five years.
- In neurology there were 10 NAS launches, including a first-in-class gene therapy for Duchenne muscular dystrophy and an antisense oligonucleotide to treat a rare form of ALS.
- Of 10 neurology launches, four drugs — cipaglucosidase alfa (Pombiliti), trofinetide (Daybue) ublituximab (Briumvi) and zuranolone (Zurzuvae) — were EBP-originated and launched.

Notes: Includes NASs launched in the U.S. in 2023. Oncology includes supportive care & diagnostics. Information collated from FDA and company releases and relevant clinical trial information. First-in-class based on FDA categorization. Any form of expedited review includes priority review, accelerated approval, breakthrough designation, or fast track determined by the FDA. If the time between the first patent filing (or start of the first clinical trial) and launch in the U.S. is less than or equal to five years this has been noted.

NAS launched in 2023 included 43 specialty drugs, 32 EBP-originated, 40 with expedited regulatory review and 29 orphan drugs

Exhibit 32: Novel active substances (NASs) launched in 2023 in the United States *continued*

***ATTRIBUTES KEY:** 1 = Oral, 2 = Biologic, 3 = Specialty, 4 = Next-gen biotherapeutic, 5 = Orphan, 6 = First-in-class, 7 = Expedited review, 8 = U.S Patent to launch ≤5 years 9 = EBP originated, 10 = EBP launched

THERAPY AREA	INDICATION	MOLECULE	BRAND	ATTRIBUTES* 1	2	3	4	5	6	7	8	9	10
Infectious diseases	Candidemia and invasive candidemia	rezafungin	Rezzayo					●		●		●	●
	COVID-19	vilobelimab	Gohibic		●	●			●	●		●	●
	HIV-1	lenacapavir	Sunlenca	●		●			●	●			
	Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP)	durlobactam + sulbactam	Xacduro							●			●
	Smallpox disease	brincidofovir	Tembexa	●				●		●			●
Endocrinology	Pediatric growth hormone deficiency	somatrogon	Ngenla			●		●				●	
	Type 1 diabetes	donislecel	Lantidra		●	●	●	●	●				●
	Type 2 diabetes	bexagliflozin	Brenzavvy	●								●	●
Immunology	Plaque psoriasis	bimekizumab	Bimzelx		●	●							
	Ulcerative colitis	mirikizumab	Omvoh		●	●							
	Ulcerative colitis	etrasimod	Velsipity	●		●						●	
Dermatology	Dystrophic epidermolysis bullosa	beremagene geperpavec	Vyjuvek		●	●	●	●	●	●		●	●
	Eschar in deep partial thickness or full thickness thermal burns	anacaulase	Nexobrid		●			●				●	●
	Severe alopecia areata	ritlecitinib	Litfulo			●							
Hematology	Anemia due to chronic kidney disease	daprodustat	Jesduvroq	●					●				
	Hemophilia A	valoctocogene roxaparvovec	Roctavian		●	●	●	●	●	●			
	Hemophilia A	efanesoctocog alfa	Altuviiio		●	●		●	●	●		●	
Eye/ear	Age-related macular degeneration	avacincaptad pegol	Izervay		●	●				●		●	●
	Demodex blepharitis	lotilaner	Xdemvy						●			●	●
	Dry eye Disease	perfluorohexyloctane	Miebo						●			●	
Respiratory	Respiratory syncytial virus (RSV)	rsv vaccine	Arexvy		●				●	●			
	Respiratory syncytial virus (RSV) and Lower respiratory tract disease (LRTD)	nirsevimab	Beyfortus		●	●				●		●	
Cardiovascular	Heart failure	sotagliflozin	Inpefa	●								●	●
	Proteinuria in primary immunoglobulin A nephropathy (IgAN)	sparsentan	Filspari	●		●		●	●	●			●
Others	Fabry disease	pegunigalsidase alfa	Elfabrio		●	●				●			
	Fibrodysplasia ossificans progressiva (FOP)	palovarotene	Sohonos					●	●	●			
	Vasomotor symptoms caused by menopause	fezolinetant	Veozah	●					●	●		●	
Totals				20	26	43	7	29	24	40	2	32	27

...table continued from the previous page

Source: IQVIA Institute, Jan 2024.

- Of the five new drugs introduced for infectious diseases, two are orphan drugs, each designed for the treatment of candidemia and smallpox. Additionally, two first-in-class drugs were launched: vilobelimab (Gohibic) for treating COVID-19 in hospitalized adults and lenacapavir (Sunlenca) for adults with multi-drug resistant HIV.
- Three specialty drugs were introduced in the field of immunology. Two of these are treatment options for ulcerative colitis, one being an injectable and the other an oral treatment.
- Within dermatology, three new drugs were launched; one is a gene therapy for dystrophic epidermolysis bullosa, and another is specifically designed for burn treatment.
- Within hematology, two hemophilia A drugs were launched, of which one is a gene therapy.

Notes: Includes NASs launched in the U.S. in 2023. Oncology includes supportive care & diagnostics. Information collated from FDA and company releases and relevant clinical trial information. First-in-class based on FDA categorization. Any form of expedited review includes priority review, accelerated approval, breakthrough designation, or fast track determined by the FDA. If the time between the first patent filing (or start of the first clinical trial) and launch in the U.S. is less than or equal to five years this has been noted.

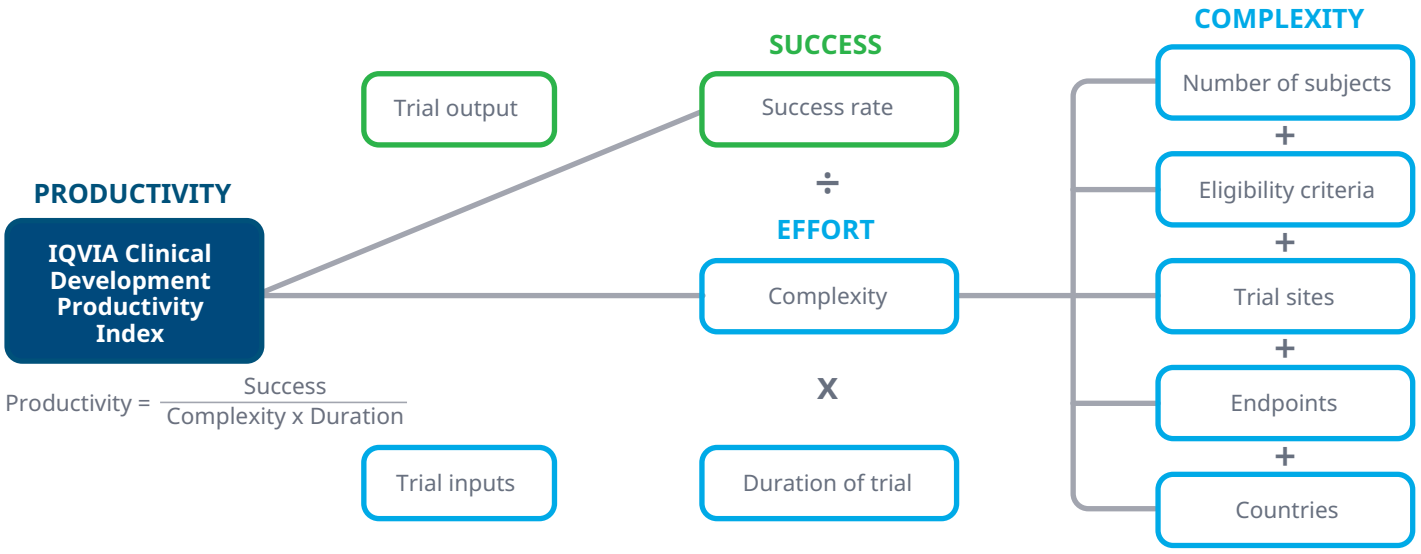
Clinical development productivity

- A Clinical Development Productivity Index provides a composite metric that combines success rates, clinical trial complexity, and trial duration on an annual basis.
- Clinical development productivity reached 17.4 compared to the 2010 level of productivity is 20, continuing a rebound from the low of 12.8 in 2020 and returning to the level seen in 2017, with most of the increase in 2023 driven by an increase in success rates.
- The composite success rate across all therapy areas rose to 10.8% in 2023 driven by increases in Phase I, Phase III and regulatory success.
- Composite success rate trends varied across disease areas in 2023 with significant increases in oncology and rare diseases.
- Clinical trial complexity increased in 2023, returning to levels seen in 2020 but with variations among the elements.
- The declining number of countries and sites for rare diseases and oncology trials is a key driver of the decrease in overall complexity.
- The average number of countries in trials has been declining, more markedly in Phase II and III studies, and including a marked shift to single-country studies even in later phases, and rationalization to fewer countries in multi-country studies.
- Emerging biopharma companies are running more single country trials than large pharma, with China trials driving recent trends.
- The total number of clinical trial subjects dropped to 1.5 million in 2023 due to a decline in COVID-19 enrollment.
- Trial durations have declined while the 'white space' before starting a subsequent research phase has increased, resulting in overall increases in development timelines.
- Nineteen drugs were launched less than five years into their patent terms in the past four years, up from eight in total from 2014–2019.
- Median overall development duration was two to four years faster when expedited regulatory pathways were used, and is generally shorter for biologics, orphan, and specialty drugs.

Industry-wide clinical development productivity rose primarily through better success rates, which rose from historic lows to the highest level since 2018. Efforts to manage trial complexity and durations have had more mixed results.

A Clinical Development Productivity Index provides a composite metric of success rates, clinical trial complexity and trial duration

Exhibit 33: Clinical Development Productivity Index

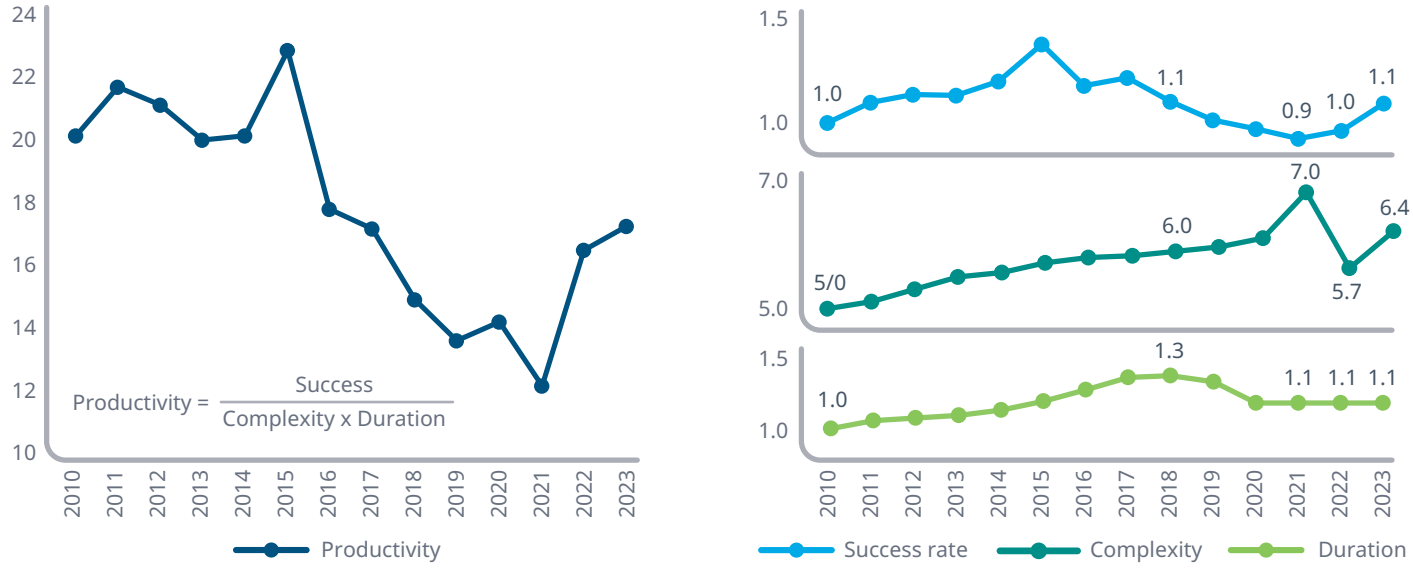


Source: IQVIA Institute, Jan 2024.

- The productivity of the clinical development process can be considered as a measure of trial outputs (drugs, innovation, trial success) compared to a measure of trial inputs or resources dedicated to obtaining those outputs (e.g., aspects of trial complexity, duration, monetary investments). Such measures of success, complexity and trial duration were selected for inclusion in the Clinical Development Productivity Index as described above.
- Increases in success will increase productivity overall as will decreases in complexity or duration; conversely, decreases in success will drive down the Clinical Development Productivity Index, as will increases in complexity and duration.
- To obtain current-state measures of trial complexity (mean number of endpoints, sites, countries, patients, eligibility criteria) as well as data on trial duration, attributes were leveraged from the Citeline Trialtrove clinical trial database. To determine the number of eligibility criteria and endpoints from the unstructured or semi-structured text in trial records, natural language processing was used to identify common formatting patterns employed by trial sponsors in detailing these features. Success metrics were calculated from IQVIA Pipeline Intelligence based on medicines progressing to a subsequent research phase or being discontinued, suspended, withdrawn, or becoming inactive for three or more years (see Methodology). Each metric in each phase for each disease is indexed to the equivalent 2010 value for all diseases. Indices are available for each phase or as an average across phases.
- An analysis of productivity was conducted across all trials started between 2010 and 2023, with details included for therapy areas: cardiovascular, dermatology, infectious diseases, endocrinology, immunology, neurology, oncology, respiratory, vaccines (separately from infectious diseases), and rare diseases.

Clinical development productivity continued to increase in 2023 driven by an increase in success rates

Exhibit 34: Clinical Development Productivity Index and elements of productivity indexed to 2010 values



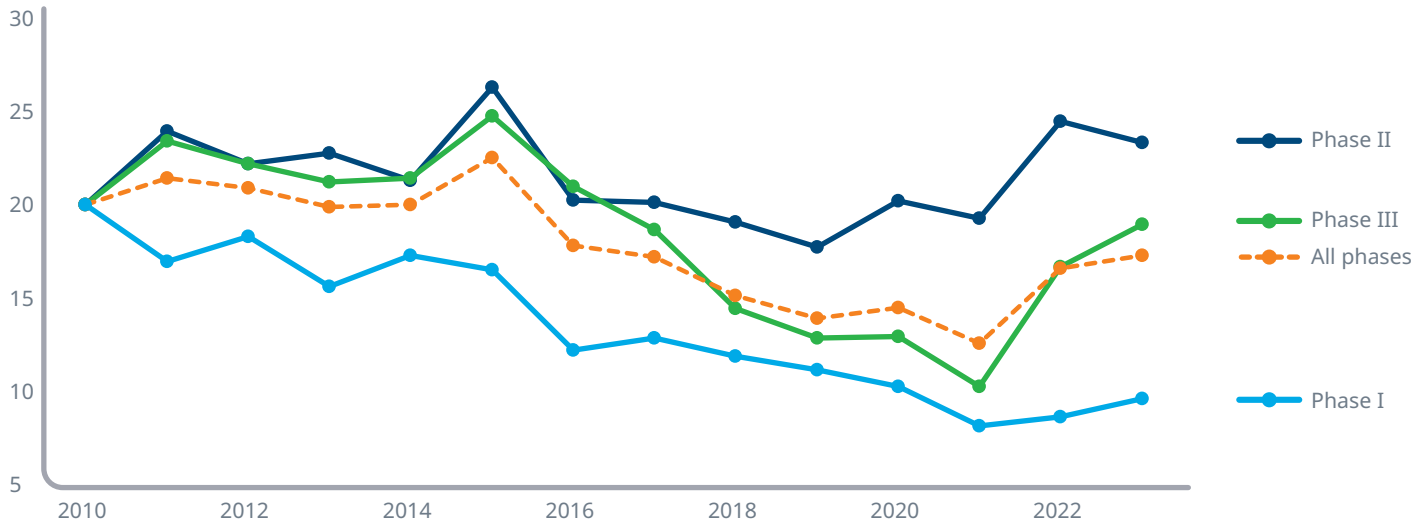
Source: IQVIA Pipeline Intelligence, Dec 2023; Citeline Trialtrove, IQVIA Institute, Jan 2024.

- Clinical development productivity — a composite metric of success rates, clinical trial complexity and trial duration — rebounded in 2022 and 2023, reversing a 10-year downward trend.
- Specifically, clinical development productivity reached 17.4 compared to the 2010 level of productivity of 20, continuing a rebound from the low of 12.8 in 2021 and returning to the level seen in 2017, with most of the increase in 2023 driven by productivity increases in Phase II and III trials as well as in success rates.
- Composite success rates nearly doubled to 10.8% from 5.8% in 2022 and while not back to the highs earlier in the decade, represent a significant improvement.
- Trial complexity returned to the previous trend of 2020 at 6.4 after dropping sharply in 2022 to 5.7 from the unusual outlier high of 7.0 in 2021, which were driven by larger numbers of study subjects for COVID-19 trials. All other components of the complexity indices increased slightly in 2023.
- Trial durations have remained essentially flat in the last four years, reflecting difficulties in recruiting patients for more rare diseases and longer follow-up periods after treatment, even as some trials have been exceptionally faster than historic norms.

Notes: Success rates and durations are indexed to the mean value for all diseases in 2010 equal to 1. The five complexity metrics are indexed to all diseases in 2010 equal to 1, and then summed, equaling 5. Data source relies on company reported information about ongoing or planned clinical trials. Substantial lags have been noted in the reporting of numbers of subjects, sites, and countries which all rely on site selection, startup, and recruitment and early trial information may not reflect the full extent of the effort required. Therefore, subjects, sites, and countries have been adjusted in the most recent year (2023) based on historic observations of this data latency. The most recent year is subject to change in subsequent periods.

The composite Clinical Development Productivity Index remained flat in 2023, with a Phase II decline offset by Phase III increase

Exhibit 35: Clinical development productivity by phase and overall, 2010–2023



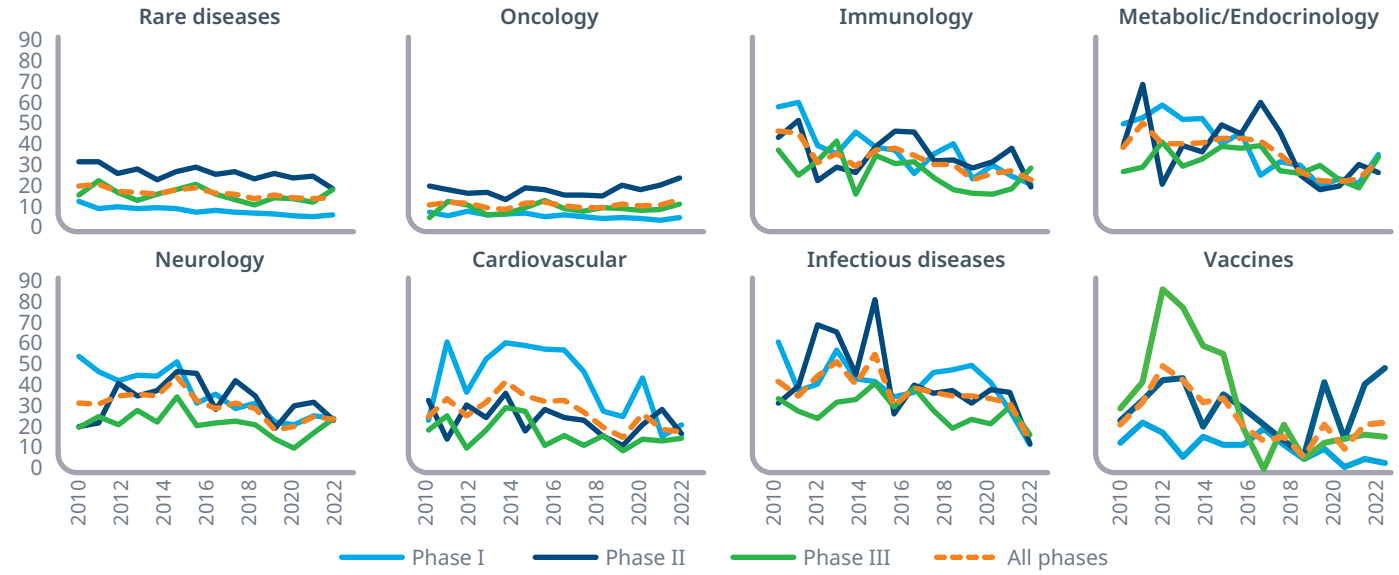
Source: IQVIA Pipeline Intelligence, Dec 2023; Citeline Trialtrove, IQVIA Institute, Jan 2024.

- The composite Clinical Development Productivity Index has slightly increased in 2023 but continues to remain low, with a drop of more than 12% over the past decade.
- All phases of clinical development showed a rebound from the low in productivity in 2021, lifting overall productivity from 12.8 to 17.4, where index is based on comparisons to 2010, set at 20.
- Phase III trials had seen a significant decline in productivity over the past five years, primarily due to decreasing probability of success and increasing durations but rebounded in the past two years as complexity dropped in 2022.
- Phase II trials have consistently been above the overall index as success rates have remained more stable and trial durations have increased slightly, but success rates decreased in Phase II in 2023, lowering overall productivity.
- While there is a great variability among therapy areas, the overall downward trend in productivity is believed to be a result of slowly increasing clinical trial timelines and decreasing probability of success, even as clinical trial complexity has seen modest reductions in recent years, and the 2023 near-doubling of success rates has therefore had a marked effect on overall productivity.

Notes: Terminated and withdrawn trials were excluded from the analysis. Trials were industry sponsored and interventional. Diagnostics, behavioral therapies, supplements, devices, and medical procedures were excluded. Data source relies on company reported information about ongoing or planned clinical trials. Substantial lags have been noted in the reporting of numbers of subjects, sites, and countries which all rely on site selection, startup, and recruitment and early trial information may not reflect the full extent of the effort required. Therefore, subjects, sites, and countries have been adjusted in the most recent year (2023) based on historic observations of this data latency. The most recent year is subject to change in subsequent periods.

Clinical development productivity indices were highest for metabolic and endocrinology while oncology extends trend as lowest

Exhibit 36: Clinical development productivity across all phases by therapy area, 2010–2023



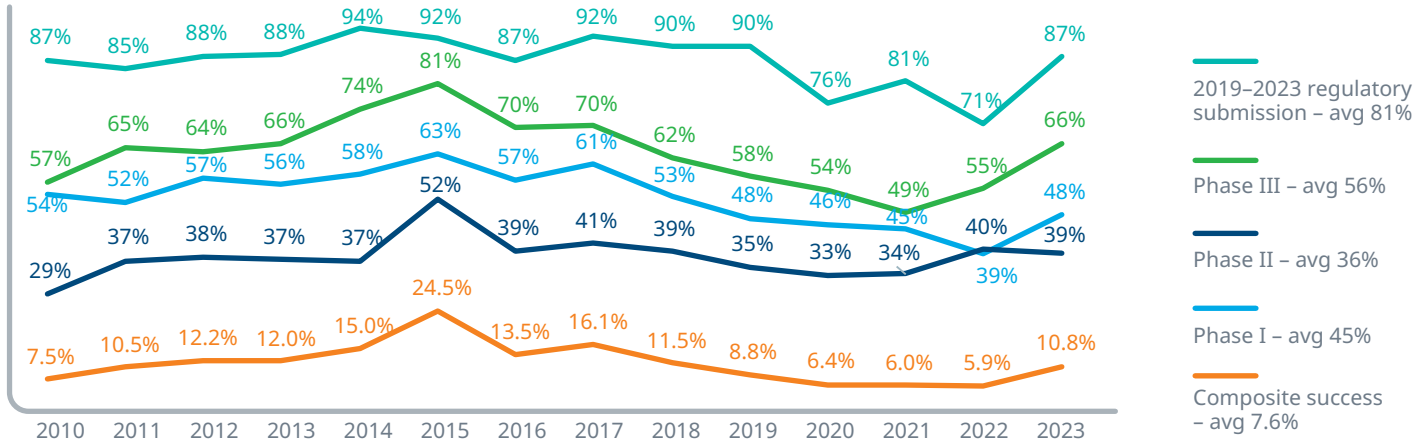
Source: IQVIA Pipeline Intelligence, Dec 2023; Citeline Trialtrove, IQVIA Institute, Jan 2024.

- The Clinical Development Productivity Index varies widely across therapeutic areas, with a low of 11.6 for oncology and a high of 28.5 for metabolic/endocrinology.
- While productivity rates in 2023 have rebounded for rare diseases due to an increase in Phase III and an increase across all phases for oncology, both have consistently had among the lowest productivity rates across the last 10 years. These areas show significant overlap and are kept to a modest productivity based on similar increases in complexity and duration.
- After vaccine productivity substantially jumped in 2022, driven by higher success rates in Phase II, it only slightly increased in 2023, offset by a dip in Phase I.
- Cardiovascular products have continued to decrease in productivity in 2023 after an initial drop the previous year, resuming the downward trend over the past decade.
- Infectious disease productivity for all phases significantly dropped from its previous year by almost 18 points in 2023 and by almost 37 points in the past decade.
- Similarly, immunology has dropped in productivity for all phases from its previous year by almost four points in 2023, due to a drop in Phase II productivity.

Notes: Terminated and withdrawn trials were excluded from the analysis. Trials were industry sponsored and interventional. Diagnostics, behavioral therapies, supplements, devices, and medical procedures were excluded. Data source relies on company reported information about ongoing or planned clinical trials. Substantial lags have been noted in the reporting of numbers of subjects, sites, and countries which all rely on site selection, startup, and recruitment and early trial information may not reflect the full extent of the effort required. Therefore, subjects, sites, and countries have been adjusted in the most recent year (2023) based on historic observations of this data latency. The most recent year is subject to change in subsequent periods.

The composite success rate rose to 10.8% in 2023 driven by increases in Phase I, Phase III and regulatory success

Exhibit 37: R&D composite success rate and average phase success rates Phase I to filing, 2010–2023



$$\text{Phase success \%} = \frac{\text{Success (drug reaches any higher phase)}}{\text{Total of success and failure}}$$

Composite success % = Phase I x Phase II x Phase III x Regulatory submissions

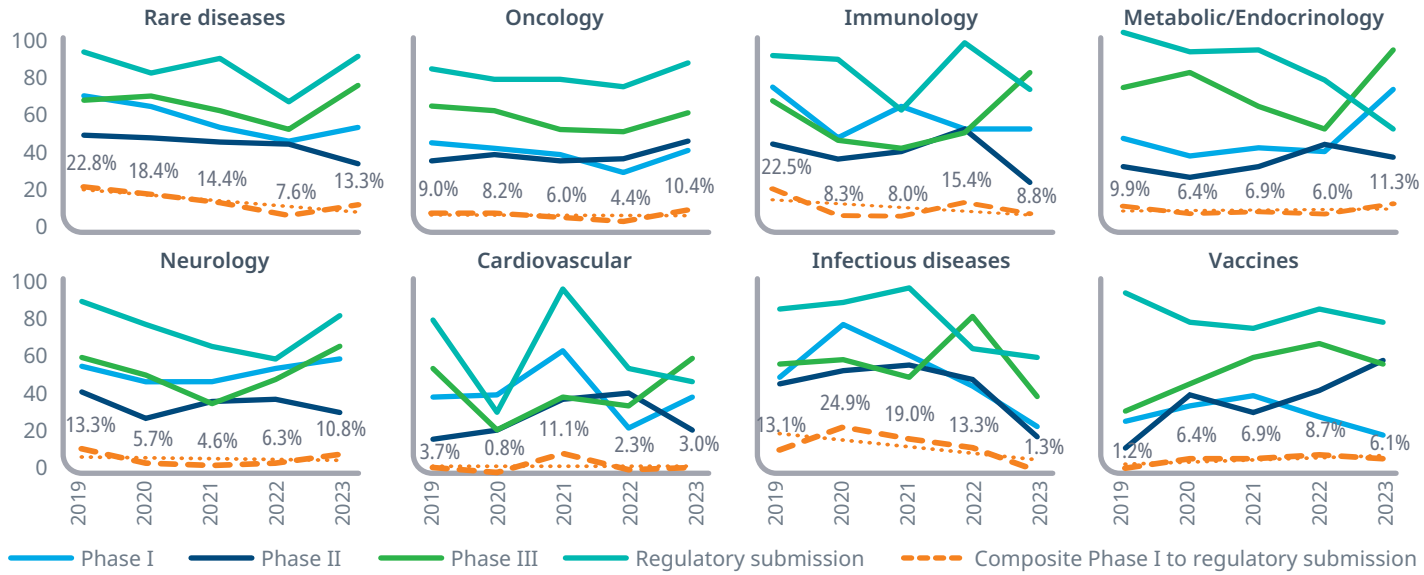
Source: IQVIA Pipeline Intelligence, Dec 2023; IQVIA Institute, Jan 2024.

- The composite success rate for the pipeline jumped in 2023 to 10.8% across all therapy areas after falling to a 10-year low in 2022, driven by increases in Phase I, Phase III and regulatory success.
- Phase I success rates rose to 48%, a level last seen in 2019.
- Phase III rates rose to 66%, far above the 56% 10-year pre-pandemic average.
- Phase II success rates remained stable at 39% in one year, returning to the level last seen in 2018 and staying close to the 36% 10-year pre-pandemic average.
- Success rates for products filing for regulatory approval reached a significant high, jumping to 87% from a low of 71% in 2022.
- These shifts in success rates have varied across therapy areas (Exhibit 38).

Notes: Phase success rates are calculated as the percentage of products reaching a subsequent phase in the year out of the total of products with an outcome including those which are discontinued, suspended or withdrawn as well as those which have been inactive for three years. The date three years after the last update determines which year the drug is considered to have gone inactive and become included in the denominator of the success rate, except when desk research has concluded the drug is still in active research. Failures due to inactivity have been adjusted based on data quality error rates for each phase. Some trials which were understood to have failed in recent years due to extended inactivity had actually been continuing and have now completed successfully, while others which were thought to be ongoing have now completed, resulting in retroactive restatement of past years success rates. The overall composite success rate in last year's report was 6.3% in 2022, compared to the restated 5.9% in the current analysis.

Composite success rate trends varied across disease areas in 2023 with significant increases in oncology and rare diseases

Exhibit 38: R&D phase and composite success rates by therapy area, 2019–2023



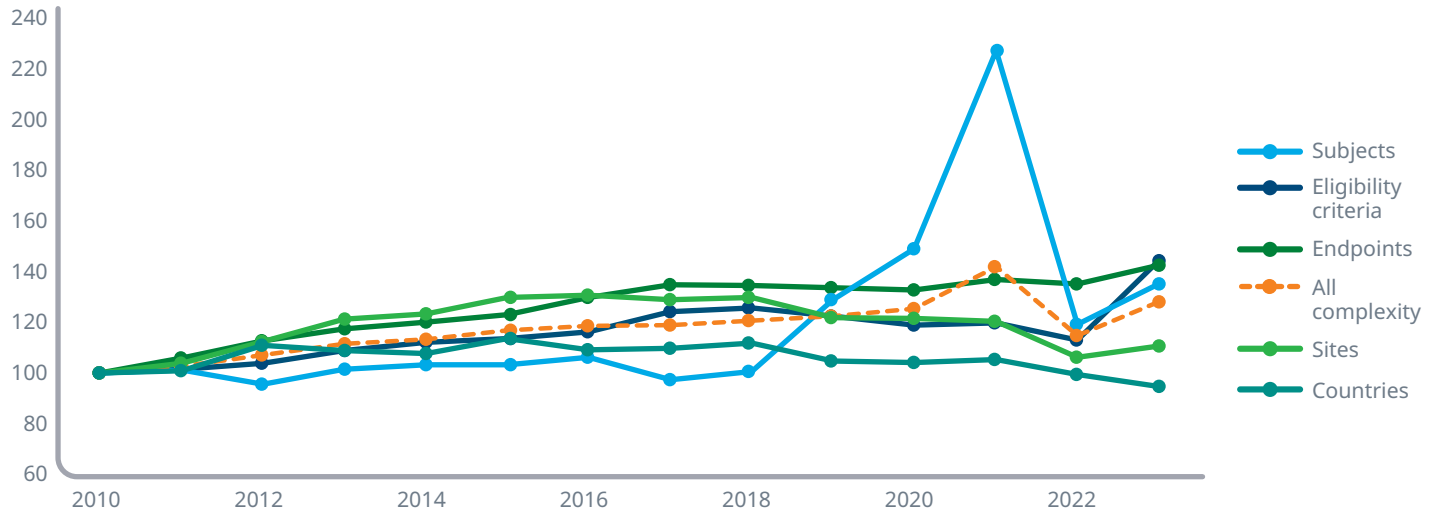
Source: IQVIA Pipeline Intelligence, Dec 2023; IQVIA Institute, Jan 2024.

- Composite success rate trends varied across disease areas in 2023, with significant increases in oncology and rare diseases.
- The composite success rate of 10.8% in 2023 was lower than the 10-year trendline in neurology, rare diseases, immunology, metabolic/endocrinology, infectious diseases, and cardiovascular classes.
- Most disease areas improved in 2023, as almost all had prior years restated by new progress in research or updated activity previously thought to have become inactive.
- While activity levels remained resilient during the pandemic, oncology, rare diseases, and neurology — the three largest segments of the R&D pipeline — all saw substantial increases in composite success rates in 2023, breaking a trend over recent years.
- Metabolic/endocrinology posted a significant increase in the Phase III success rate, pointing to further potential approvals in this dynamic area.
- Vaccines, which had seen significant increasing success from 2019 to 2022, saw decreasing in success except in Phase II in 2023, mostly driven by the previous years' success of Phase I trials.
- Infectious diseases composite success declined significantly in 2023 — by 12 percentage points to only 1.3% — continuing below the trendline for the observed period, driven by declines in all phases and offset by regulatory submission successes.

Notes: Phase success rates are calculated as the percentage of products reaching a subsequent phase in the year out of the total of products with an outcome including those which are discontinued, suspended or withdrawn as well as those which have been inactive for three years. The date three years after the last update determines which year the drug is considered to have gone inactive and become included in the denominator of the success rate, except when desk research has concluded the drug is still in active research. Infectious diseases excludes vaccines.

Clinical trial complexity increased in 2023, returning to levels seen in 2020 but with variations among the elements

Exhibit 39: Elements of complexity indexed to 2010 values, all phases 2010–2023



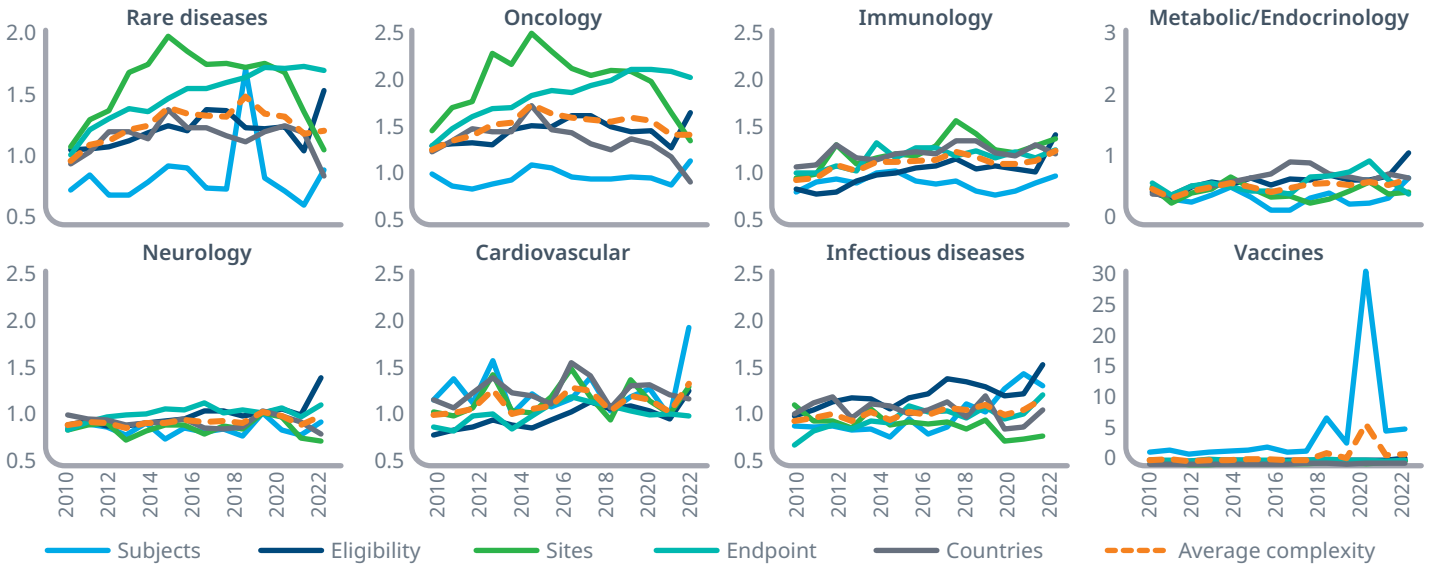
Source: Citeline Trialtrove, IQVIA Institute, Jan 2024.

- Following a period of increasing complexity in the first half of the last decade, trial complexity dipped in 2022 to an index of 114.3 compared to 2021 before jumping back to 127.3 in 2023, while still generally exceeding prior years.
- The number of trial subjects increased in 2023 and exceeded all non-pandemic years in the past decade, being the main driver of a modestly higher overall complexity in 2023, shared with a slight increase in eligibility requirements, endpoints, sites and number of subjects.
- The decrease in the number of countries across industry trials was the only complexity driver to decline in 2023, with countries 5% below 2010 levels.
- The number of clinical trial subjects on average has increased dramatically since 2018, with the 2022 index of 119 and 2023 at 134, both resulting from large-scale COVID-19 vaccine trials.
- These measures, while not definitive in determining the complexity of operating a trial, do provide a useful guide for the ongoing effort associated with trials.

Notes: Terminated and withdrawn trials were excluded from the analysis. Trials were industry sponsored and interventional. Diagnostics, behavioral therapies, supplements, devices, and medical procedures were excluded. Data source relies on company reported information about ongoing or planned clinical trials. Substantial lags have been noted in the reporting of numbers of subjects, sites, and countries which all rely on site selection, startup, and recruitment and early trial information may not reflect the full extent of the effort required. Therefore, subjects, sites, and countries have been adjusted in the most recent year (2023) based on historic observations of this data latency. The most recent year is subject to change in subsequent periods.

Complexity increased across all diseases in 2023 driven by an increasing number of eligibility criteria

Exhibit 40: Trial complexity by element and therapy area, 2010–2023



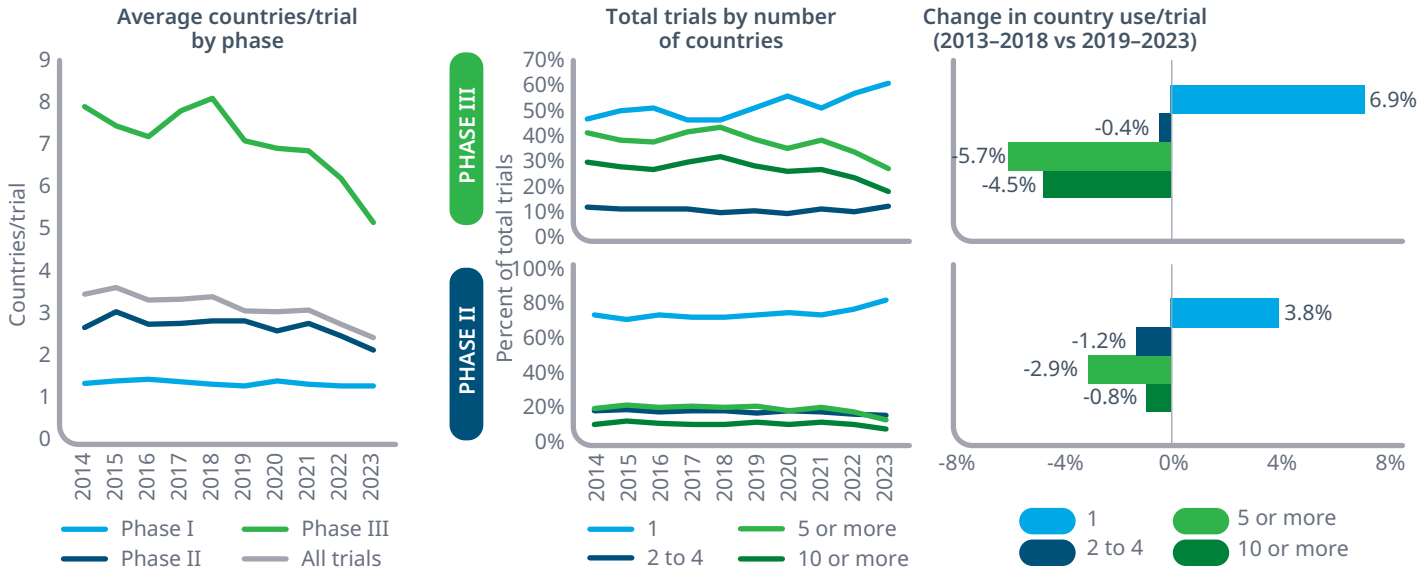
Source: Citeline Trialtrove, IQVIA Institute, Jan 2024.

- The declining number of countries and sites for rare diseases and oncology trials is a key driver of the decrease in overall complexity in 2023.
- Oncology trials, which are among the most complex using the index, saw a drop in complexity in 2023 to their lowest level since 2010. As with the pipeline in general, this drop is highly correlated with the drop in number of sites and countries, which began in 2015 but was amplified by the pandemic.
- The index of eligibility based on inclusion and exclusion criteria in trials increased in 2023, related to a shift in the mix of trials away from rare cancers (Exhibit 15).
- Rare disease trials increased in complexity in 2023, breaking away from a declining trend since 2019 due to a declining number of sites and countries and an uptake in the number of subjects, indicating a geographic focus on selected smaller patient populations with the exception of large Ebola trials started in 2019. Fewer sites for rare disease trials was a notable inflection in the last four years.
- While vaccine trials became increasingly larger than other trials and varied considerably in the number of subjects by disease target, the much larger trials in Ebola, influenza and COVID-19, the spike in 2022 led to a return to normal levels in 2023.

Notes: Terminated and withdrawn trials were excluded from the analysis. Trials were industry sponsored and interventional. Diagnostics, behavioral therapies, supplements, devices, and medical procedures were excluded. Infectious diseases excludes vaccines. Substantial lags have been noted in the reporting of numbers of subjects, sites, and countries which all rely on site selection, startup, and recruitment and early trial information may not reflect the full extent of the effort required. Therefore, subjects, sites, and countries have been adjusted in the most recent year (2023) based on historic observations of this data latency. The most recent year is subject to change in subsequent periods.

Country utilization per trial is declining — especially in Phase II and III where number of single-country trials are rising

Exhibit 41: Country utilization across all phases of industry interventional trials, 2014–2023



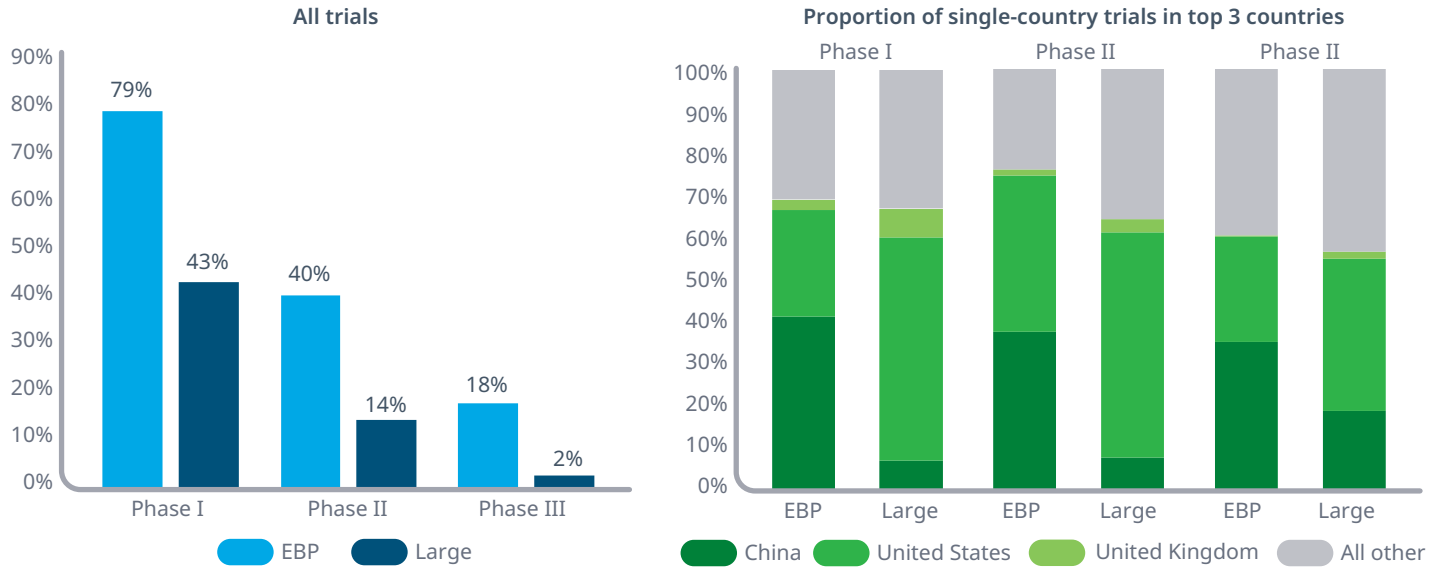
Source: Citeline Trialtrove, IQVIA Institute, Jan 2024.

- There has been a significant decrease in number of countries per trial, driven by notable country-use decreases in Phase II and Phase III trials.
- Phase III country uses per trial dropped by 35% from 2014 to 2023, while Phase II country use dropped by 20% and Phase I dropped by 5%.
- An increase in single country trials in Phase II and Phase III trials is a fundamental driver of the decreasing country utilization, as the most recent five-year average Phase III single-country utilization was up 6.9% from the first five years of the analyzed decade and the Phase II single-country utilization was up by 3.8%.
- Taken together, the accumulated decrease in the number of countries per trial is contributing to a lower trial complexity and an overall productivity increase.
- Sponsors may choose to include differing numbers of countries in trials for a variety of reasons linked to disease prevalence variations across countries, regulatory requirements, or their own capabilities and relationships with trial sites.
- These variations in the short term are less informative but longer-term trends point to more consistent shifts in the decisions being made across sponsors.

Notes: Trials were industry sponsored and interventional. Diagnostics, behavioral therapies, supplements, devices, and medical procedures were excluded. Substantial lags have been noted in the reporting of numbers of subjects, sites, and countries which all rely on site selection, startup, and recruitment and early trial information may not reflect the full extent of the effort required. Therefore, the average number of countries per trial have been adjusted in the most recent year (2023) based on historic observations of this data latency. The total number of countries used for trial counts were not adjusted. The most recent year is subject to change in subsequent periods.

Emerging biopharma running more single country trials than large pharma with China trials driving recent trend

Exhibit 42: Single-country industry interventional trials share by phase and company segment, 2021–2023



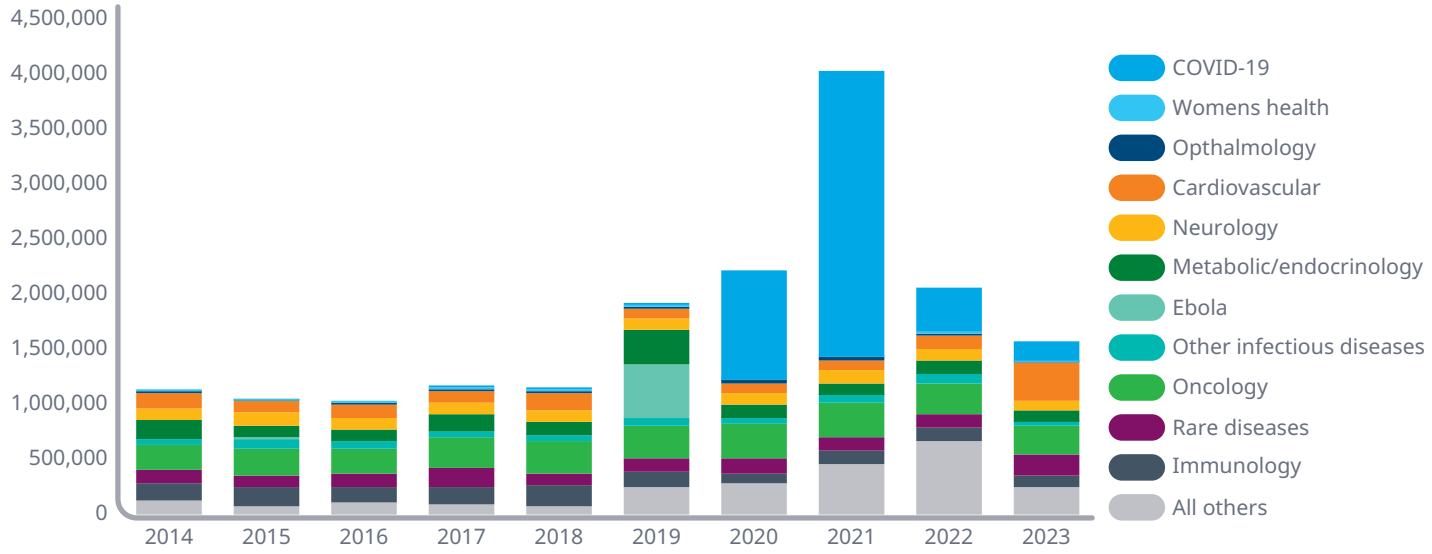
Source: Citeline Trialtrove, IQVIA Institute, Jan 2024.

- The relative number of single-country trials as a percent of total trials differs by company type and by phase for trials started in the last three years.
- Single-country trials account for nearly 80% of the EBP Phase I trials, while only 43% of large company Phase I trials are single-country.
- Similarly, 40% of EBP Phase II trials are single-country while only 14% of large company Phase II trials are; In Phase III trials, 18% of EBPs are single-country while only 2% of large company trials are single country.
- This finding aligns with the observation in exhibits 11 and 12 that nearly 30% of EBP trials in 2023 are coming from Chinese headquartered companies, and only one-quarter of these run any trials outside China. Conversely, single-country trials originated with large companies are predominantly conducted in the United States.
- The extent to which sponsors can rationalize country selection for trials is limited by the prevalence of the target disease and regulatory requirements, which have complex requirements for inclusion of subjects, especially in later phases.
- Conversely, regulators across developed countries have been more closely scrutinizing single-country trials, which do not include countries or patients similar to their own populations.

Notes: Industry interventional studies started 2021-2023. Sponsors segmentation to large (>$10Bn sales) and EBP (<$500Mn sales and <$200Mn R&D spend) and not showing analysis of small and mid-sized segments with sales between $500Mn and $10Bn. Studies are assigned to Large or EBP segment if a ponsor's segment is the same or larger than other sponsors. Large segment studies may include EBP co-sponsors but EBP segment studies do not include larger companies.

The total number of clinical trial subjects dropped to 1.5 million in 2023 due to a decline in COVID-19 enrollment

Exhibit 43: Clinical trial subjects, all phases, all diseases, 2014–2023



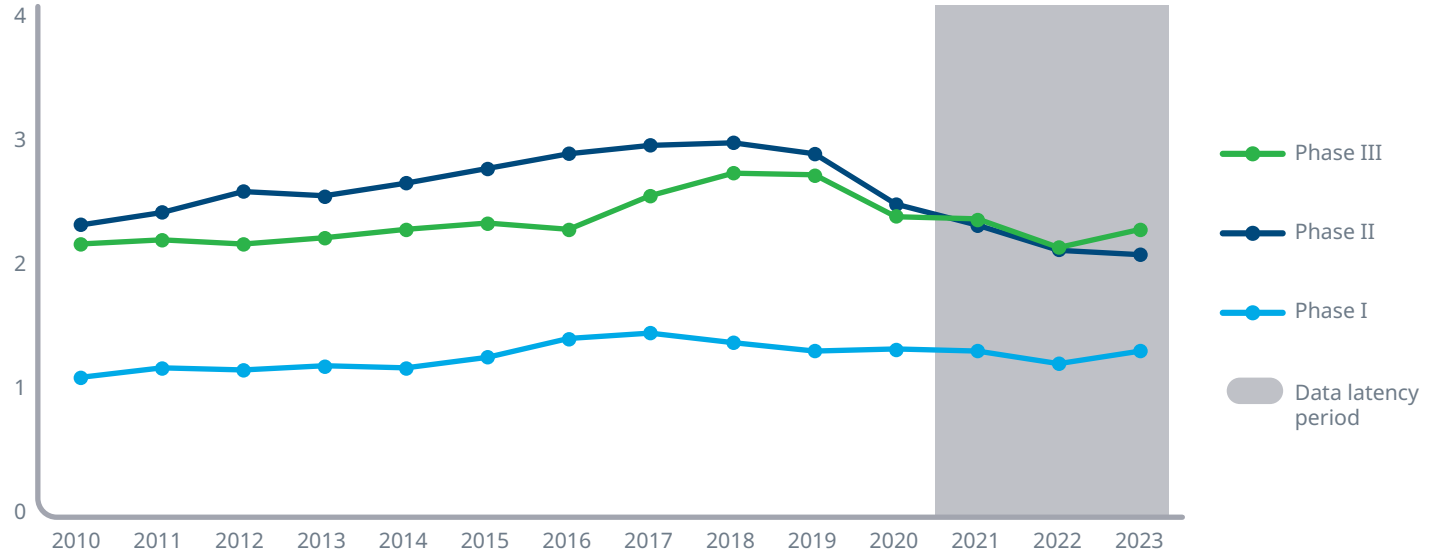
Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Jan 2024.

- While the last four years have seen record-breaking numbers of subjects planned or enrolled in clinical trials, the total number of clinical trial subjects dropped to 1.5 million in 2023 due to a decline in COVID-19 enrollment.
- The largest area of increase in study subjects has been in cardiovascular, nearly tripling to 347,000 subjects in 2023 compared to 127,000 in 2022.
- Similarly, rare diseases have also increased their number of subjects in 2023 to 186,000, up from 120,000 the previous year.
- While COVID-19 subjects reached 1 million in 2020 and another 2.4 million in 2021, studies have decreased their enrollment to 184,000 in 2023.
- Oncology trials accounted for 17% of the industry's clinical trial subjects in 2023 with 276,000 subjects, down by 7,000 subjects from 2022 but up from 8% of all trial subjects in 2021, and a lower share than the share of trials resulting from smaller average trial enrollment.
- The number of subjects in trials is generally trending down as more trials focus on niche populations, although this has been reversed with some large population trials for cardiovascular.

Notes: Subjects are the reported target or actual patients reported for trials with planned or actual start dates in each year.

Trial durations have increased slightly over the past decade, and Phase III, in particular, has been a driver in recent years

Exhibit 44: Average trial duration in years by phase, all therapy areas, 2010–2023



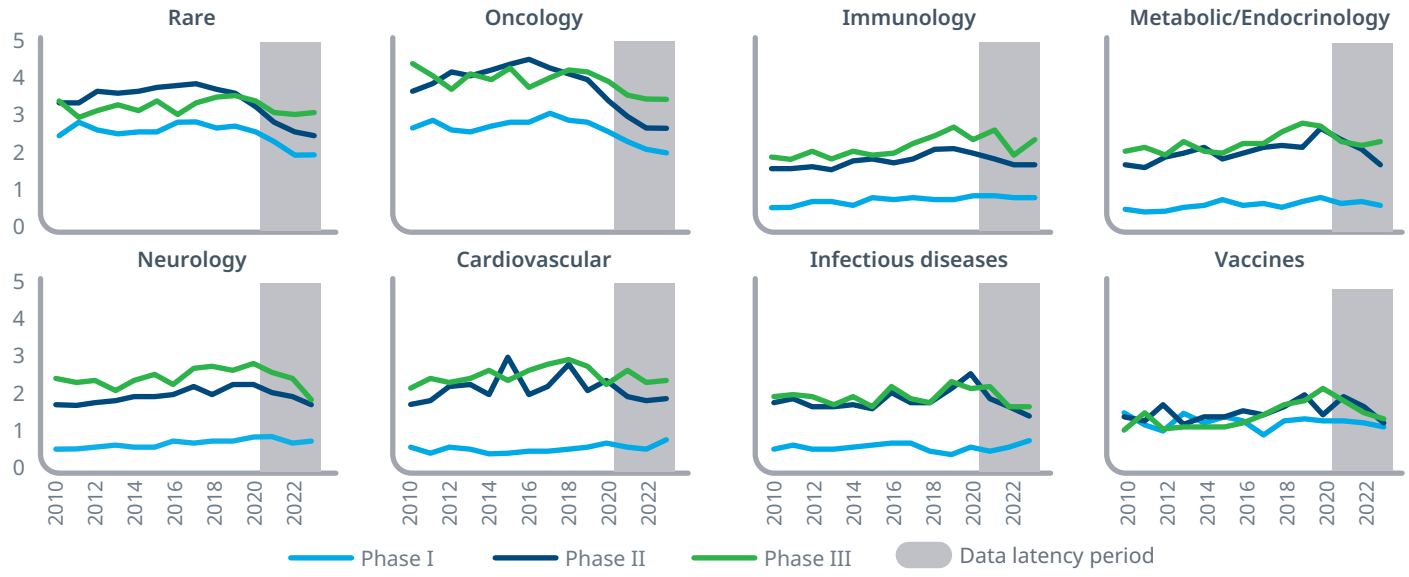
Source: Citeline Trialtrove, IQVIA Institute, Jan 2024.

- Prior to the most recent three years, the majority of trial durations were based on actual completion, whereas the most recent periods have less than 50% of trials with actual dates and include a mix of very accelerated actual trials as well as potentially unrepresentative estimates from sponsors.
- Furthermore, these durations based on estimates have typically been revised upward in subsequent updates of trial information.
- Disruptions to trial operations caused by the COVID-19 pandemic are thought to have extended trial durations, a pattern which may not yet have been reported for some studies, making the latest three years an unreliable guide to the expected trends.
- Prior to 2020, Phase III trials saw a moderate increase in trial duration — up to, on average, 2.8 years in 2019 compared to 2.2 years in 2010.
- As a result of these data latency issues, the duration information for 2019 is used for 2020 to 2022 in productivity indices elsewhere in this report, and these indices may be restated in later updates as actual durations are more reliably reported.

Notes: Trial durations are calculated as the time between trail start and the completion of the primary endpoints even as some trial activity may continue after this. In the data latency period, more than 50% of trials report planned end dates, which in combination with actual end dates that are unusually rapid, skew the durations downward in a pattern which is consistently restated over time. For analysis in the development productivity index, the last pre-latency period (2020) is used as the duration for the subsequent years.

Oncology and rare diseases trial durations have been declining in recent years, attenuating overarching trial duration increases

Exhibit 45: Average trial duration (years) by phase and therapy area, 2010–2023



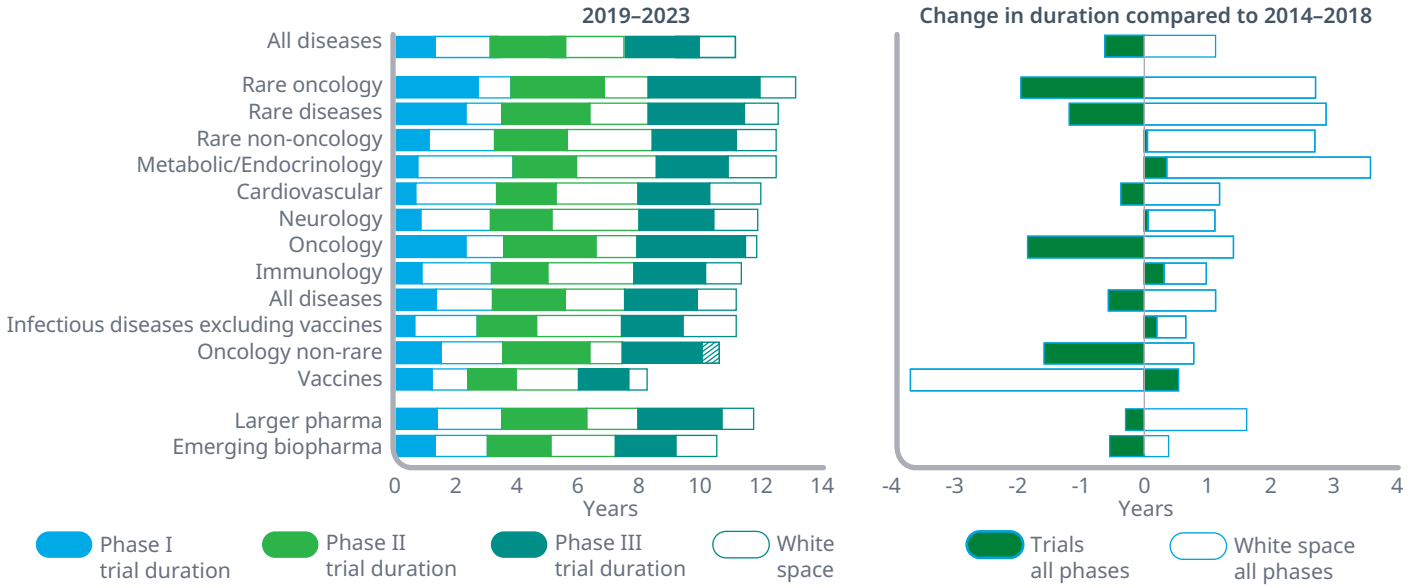
Source: Citeline Trialtrove, IQVIA Institute, Jan 2024.

- Trial durations for most disease areas have been generally stable over the last decade, except for oncology and excluding the data latency period in the last three years.
- Phase I trials are often very short, with all but oncology, rare diseases, vaccines, and dermatology averaging less than a year.
- Total (all phases) oncology duration has come down by an average of 1% per year through 2018, with Phase II trials decreasing in duration at the greatest rate.
- Oncology and rare diseases have the longest timelines in general across the disease areas, likely due to difficulties in finding and recruiting patients as well as extended observation periods to demonstrate treatment efficacy.

Notes: Terminated and withdrawn trials were excluded from the analysis. Trials were industry sponsored and interventional. Diagnostics, behavioral therapies, supplements, devices, and medical procedures were excluded. Trial duration is based on trial dates reported in clinical trial databases. Trial start date is the date on which the enrollment of participants for a clinical study began. Trial end date corresponds to when the trial ended or is expected to end. Vaccine trials are infectious disease only. Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Infectious diseases excludes vaccines.

Trial durations have declined while the 'white space' before starting a subsequent research phase has increased

Exhibit 46: Comparison of trial duration to phase-change duration (years) in key disease areas, 2014–2023



Source: IQVIA Pipeline Intelligence, Dec 2023; Citeline Trialtrove, IQVIA Institute, Jan 2024.

- On average, new drugs spend 45% of their development time on white space — the time between trial completion and starting the next phase — on the way to regulatory submission, but for trials completed in the past five years, the white space increased 14 months offsetting the seven-month reduction in trial durations and resulting in seven months longer overall durations.
- The proportion of white space varies widely across therapeutic areas, from 13% of total program duration for rare oncology to 59% for infectious disease and cardiovascular.
- While oncology has the shortest white space, it also has the longest treatment time, and the trade-off of treatment and white space timing is likely partially driven by a high percentage of adaptive trials.

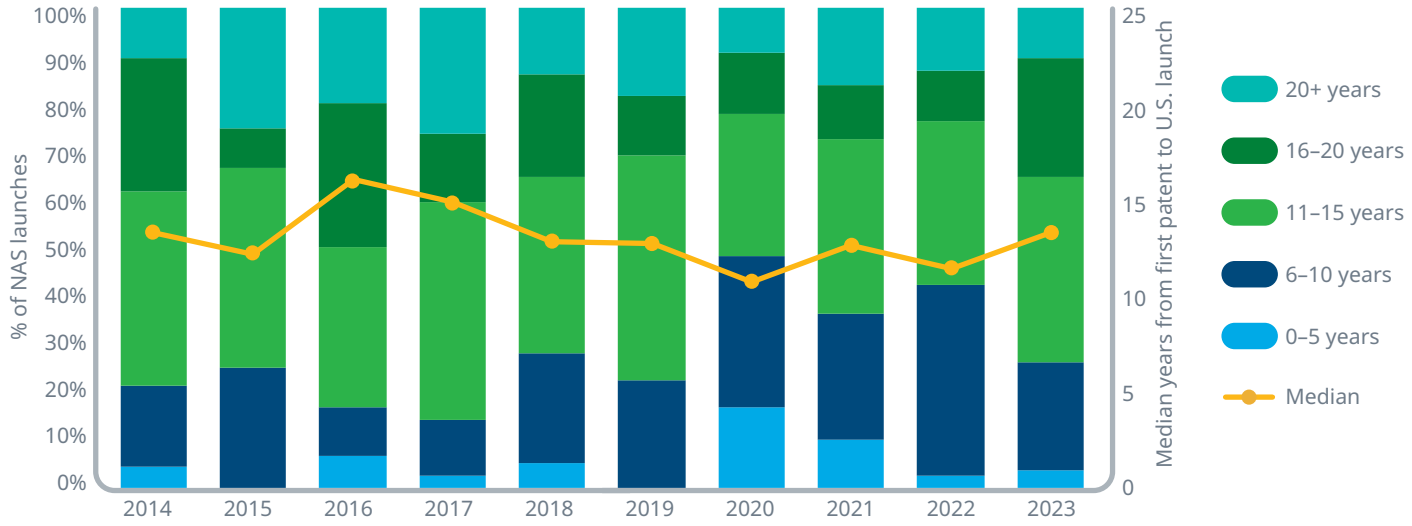
Taking trial and white space time together, the total average program duration for oncology trials is longer than more than half of the remaining therapeutic areas.

- EBP companies have almost 14.6 months (10%) faster average program timing compared to larger companies, with 19.4 months (23%) shorter trial duration and 4.8 months (8%) more white space.
- Optimizing trial durations, white space and overall duration is best exemplified by the COVID-19 trials vaccine and therapeutic trials, which demonstrated the fastest development and the least white space of any programs.

Notes: Trial duration is counted from trial start to primary completion using Citeline TrialTrove. Phase duration is counted from phase start to subsequent phase start using IQVIA Pipeline Intelligence. The difference between these durations includes a variety of sponsor activities summarized for this analysis as 'white space'. Analyzed groups are not mutually exclusive. Phase and white space durations analyzed for periods 2014-2018 and 2019-2023, displaying absolute differences in the average durations. Infectious disease therapy area excludes vaccines.

Nineteen drugs were launched less than 5 years into their patent terms in the past 4 years, up from 8 in total from 2014–2019

Exhibit 47: Time from first patent filing or human trial and U.S. launch for novel active substances, 2014–2023



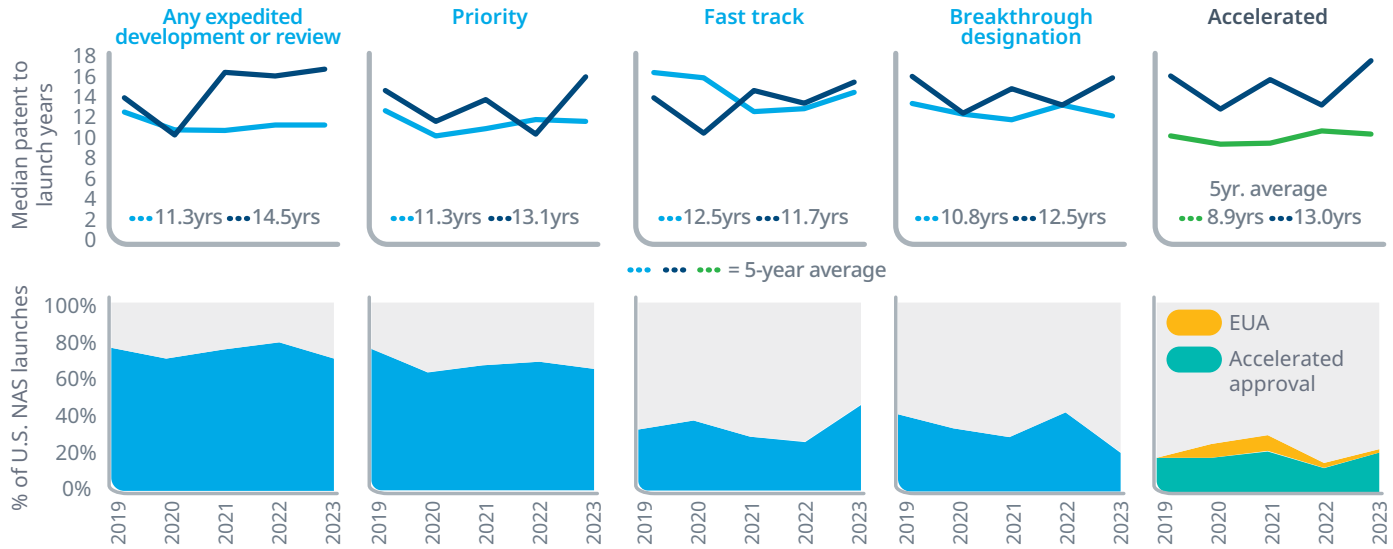
Source: IQVIA ARK Patent Intelligence, Citeline TrialTrove, IQVIA Institute, Jan 2024.

- The time from when a company first patents an innovation or starts human trials until the launch of the new medicine represents a useful proxy for the efficiency of the R&D process.
- The median time for U.S. NASs rose to 13.3 years in 2023, up from 11.4 years in 2022 and only slightly above the average of 13 years from the prior nine years.
- Out of 57 launches in the U.S., two (~4%) have less than five years from patent to U.S. launch, which includes epcoritamab (Epkinly), an oncology drug which received accelerated approval, and Flotufolastat F-18 (Posluma), a radioactive diagnostic agent for use with PET imaging for prostate cancer.
- Most of the 2023 launches, about 39%, were in the 11–15 year cohort, and just under 23% of the launches of that same year were in the 6–10-year cohort — almost 17% below the previous year.
- Examination of drug approvals across the decade in the fastest cohort shows nearly all are targeting oncology or infectious disease.
- Looking across the 10-year analysis period, 85% of the drugs in the fastest cohort were developed with at least one expedited designation or pathway as compared to the entire set of molecules launched in the time frame, with 68% use of expedited approvals.
- Only 19% of the launches in the fastest cohort were for first in class molecules compared to 42% for all launches in the decade, but in the next fastest launch cohort of 6–10 years, first-in-class molecules represented 45% of the drugs — on par with the full dataset and suggesting first-in-class does not necessarily carry a timing ‘penalty’ versus follow-on mechanisms.

Notes: Time is counted from the filing date of the first relevant patent, or the start of the first human trial whichever is earlier. Duration is calculated to the launch in the U.S, (not approval) determined through the appearance of sales volume in IQVIA audits or company statements indicating availability.

Median overall development duration was 2–4 years faster when expedited regulatory pathways were used

Exhibit 48: U.S. NAS launches and time from first patent filing or human trial approval attributes, 2019–2023



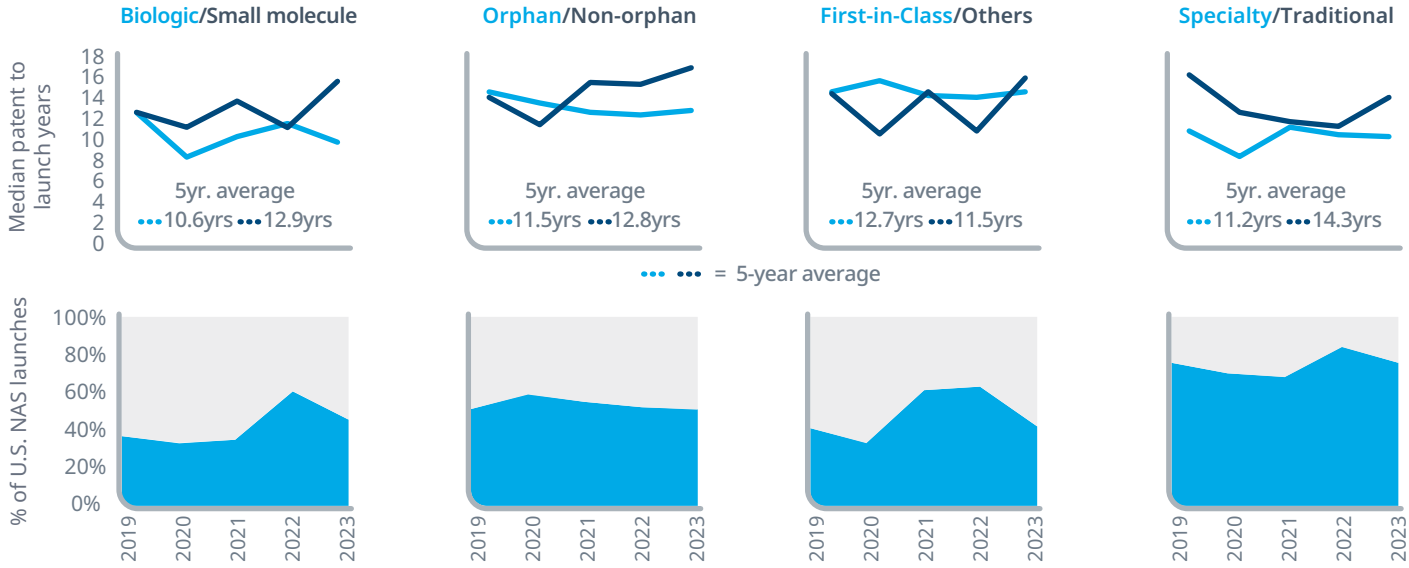
Source: IQVIA Institute, Jan 2024.

- In a continuing trend, increasing numbers of newly approved drugs have some form of expedited review in 2023, with 70% of the new launches being designated as priority, fast track, breakthrough or granted accelerated approvals.
- On average, the development timeline — the time between the first patent filing or start of the first human trial to the launch of the medicine in commercial markets — is 3.2 years faster with the various forms of expedited development or review.
- Overall, in the past five years, 73% of NAS launches have used any expedited development or review mechanism, and in 2023, fast-track and accelerated approvals rose in relative representation of U.S. NAS launches, while priority review and breakthrough designations dropped.
- Fast-track has averaged a slower duration than other drugs but would presumably have been even slower without the review acceleration.
- Accelerated approval results in launch over four years faster than drugs without it.
- Of the 57 U.S. drugs launched in 2023, 37 had priority designation, 12 were breakthrough designations, 26 were placed on the fast-track pathway, and 13 were approved through accelerated approval — including one COVID-19 NAS with Emergency Use Authorization.

Notes: A novel active substance (NAS) is a new molecular or biologic entity or combination where at least one element is new; Includes NASs launched in the United States 2019–2023 regardless of the timing of FDA approval. Time is counted from the filing date of the first relevant patent, or the start of the first human trial whichever is earlier. Duration is calculated to the launch in the U.S, (not approval) determined through the appearance of sales volume in IQVIA audits or company statements indicating availability.

Development duration from first patent or human trials until launch is generally shorter for biologics, orphan and specialty drugs

Exhibit 49: U.S. NAS launches and time from first patent filing or human trial by drug attributes, 2019–2023



Source: IQVIA Institute, Jan 2024.

- There were 26 biologic novel active substances (NASs) launched in 2023, the third straight year above 20, but the share of launches dropped to 46%, still above the 35% average for 2019-2021 and totaling 109 new drugs in the past five years.
- Biologics have development timelines — the time between first patent filing or first human trial and the launch of the medicine — that are 2.3 years faster than small molecules, linked to how some biologics target diseases with unmet needs and receive various forms of expedited review.
- There were 29 NASs launched in 2023 with orphan designations for one or more of their approved indications, more than 50% of launches for the fifth straight year, and with development timelines 1.3 years faster than non-orphan drugs.
- By contrast, first-in-class NASs have averaged a speed of 1.2 years slower to market than other drugs, potentially related to time required to expand scientific understanding in new areas. First-in-class drugs were 54% of NAS launches in the past five years, contributing to significant clinical advances across a range of disease areas as well as some longer development cycles.
- Specialty drugs are often overlapping the other segments significantly and are 3.1 years fewer than traditional drugs, likely a function of expedited reviews for drugs treating areas with high unmet needs.

Notes: A novel active substance (NAS) is a new molecular or biologic entity or combination where at least one element is new; Includes NASs launched in the United States 2019–2023 regardless of the timing of FDA approval. Time is counted from the filing date of the first relevant patent, or the start of the first human trial whichever is earlier. Duration is calculated to the launch in the U.S, (not approval) determined through the appearance of sales volume in IQVIA audits or company statements indicating availability.

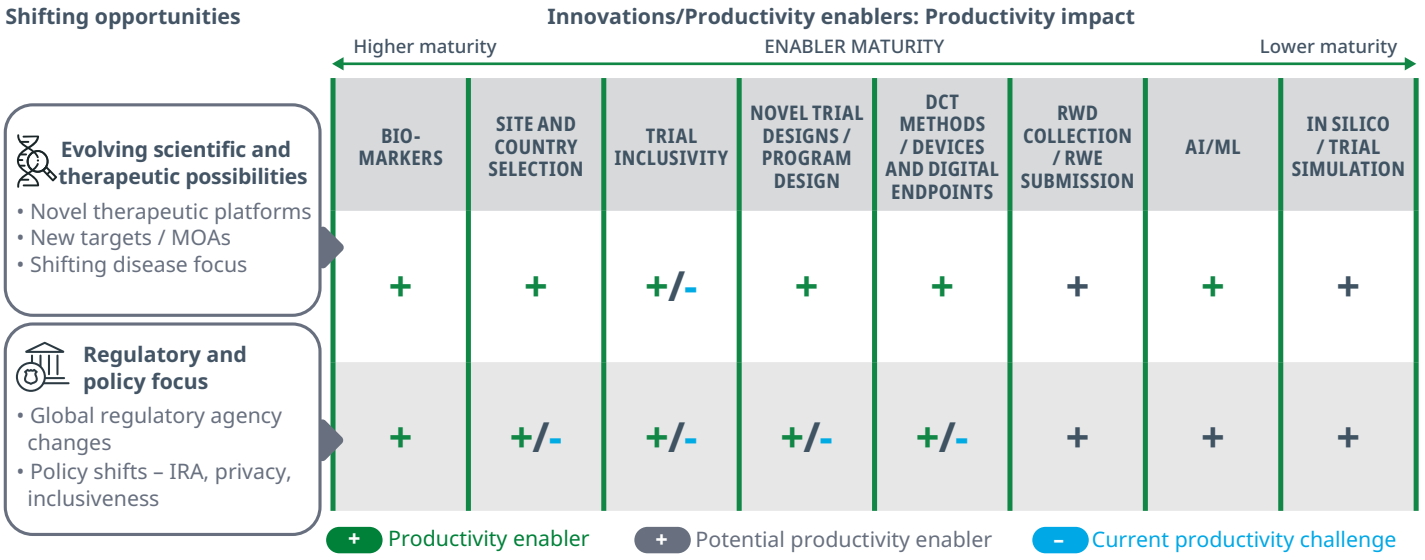
Productivity enablers

- Industry sponsors are responding to therapeutic and regulatory shifts and opportunities with a range of strategies and approaches designed to enhance or enable productivity.
- Regulatory agencies are generally undergoing positive changes across geographies, but capacity constraints are delaying implementation of consistent approaches to simplification, transparency and speed in some geographies.
- Large pharmaceutical companies generally run trials with more countries and sites, and their country-utilization over the decade is evidence of ongoing and evolving analytical focus to optimize clinical trial footprints.
- Declining inclusion of Black/African American and Hispanic patients in U.S. and global clinical trials over the last three years reflects challenges of shifting therapeutic and geographic footprint and the ongoing need for integrated trial planning.
- Clinical program design strategies including use of predictive biomarkers, single-arm trials, and combined-phases contribute to shorter development durations.
- Novel trial designs have averaged 18% of trials since 2020, led by oncology, with more than 29% novel designs
- Use of RWE evidence for U.S. regulatory approvals had been rising but dropped to only two approvals per year in the past two years, a reminder that the use of RWE is driven by submissions and the FDA's willingness to base decisions on them.
- Decentralized methodologies remain a stable feature of trial activity, albeit at a lower level after a COVID-19 driven peak in 2020.
- Clinical development programs resulting from AI utilization in discovery are maturing with an increased number of late-stage programs and examples of new indications for exiting drugs but are still to deliver a novel active substance to the market.
- Industry has been focused on minimizing regulatory setbacks in the form of complete response letters (CRLs), especially for clinical reasons, although overall rates were higher in 2023. Operational or non-clinical reasons for CRLs have been impacting emerging biopharma companies differently than larger firms.

Productivity increases may be enabled in a more transparent and simplified regulatory environment, which is being seen to varying degrees across geographies and differing adoption of strategies across companies.

Industry is responding to therapeutic and regulatory shifts and opportunities with spectrum of productivity enablers

Exhibit 50: Framework for impact of innovative productivity enablers

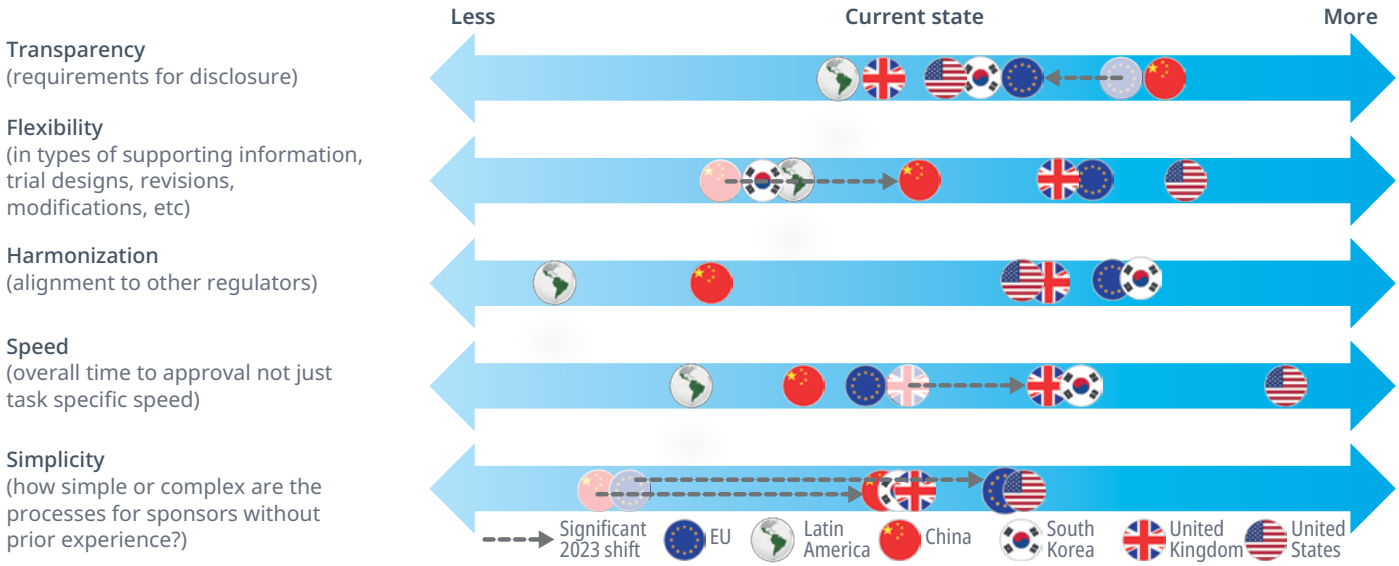


Source: IQVIA Research and Development Solutions expertise, IQVIA Institute, Jan 2024.

- Ongoing and increasing inclusion of highly complex and often novel mechanisms of action including CAGT therapies and antibody drug conjugates (ADCs) introduces technical and regulatory complexity into the industry pipeline.
- Likewise, ongoing regulatory agency and policy evolutions in major markets including the U.S., EU, UK and China are working toward improved responsiveness, but also present some challenges to industry productivity as agencies work through the complexities of these changes.
- As these complexities take hold across the pharmaceutical development pipeline, productivity is being impacted by a range of trade-off effects on complexity, timing, and probability of success and requires clinical delivery innovations and enablers to ensure that scientific and regulatory advances translate to industry productivity.
- Multiple productivity enablers, including biomarker use, strategic site and country selection, novel trial designs, decentralized methodologies, and AI/ML drug discovery show steady or increasing use in the industry pipeline in the past five years.
- Innovative enablers are demonstrating productivity gains including biomarker use, which is associated with an average of an 8.5 month decrease in time from patent filing to approval across the past five years, and an average nearly two-year efficiency for flexible development programs with combined Phase I and II trials.

Global regulatory agency characteristics continue to differ across geographies as improvement efforts begin to take hold

Exhibit 51: Comparative analysis of key characteristics of global pharmaceutical regulatory agencies

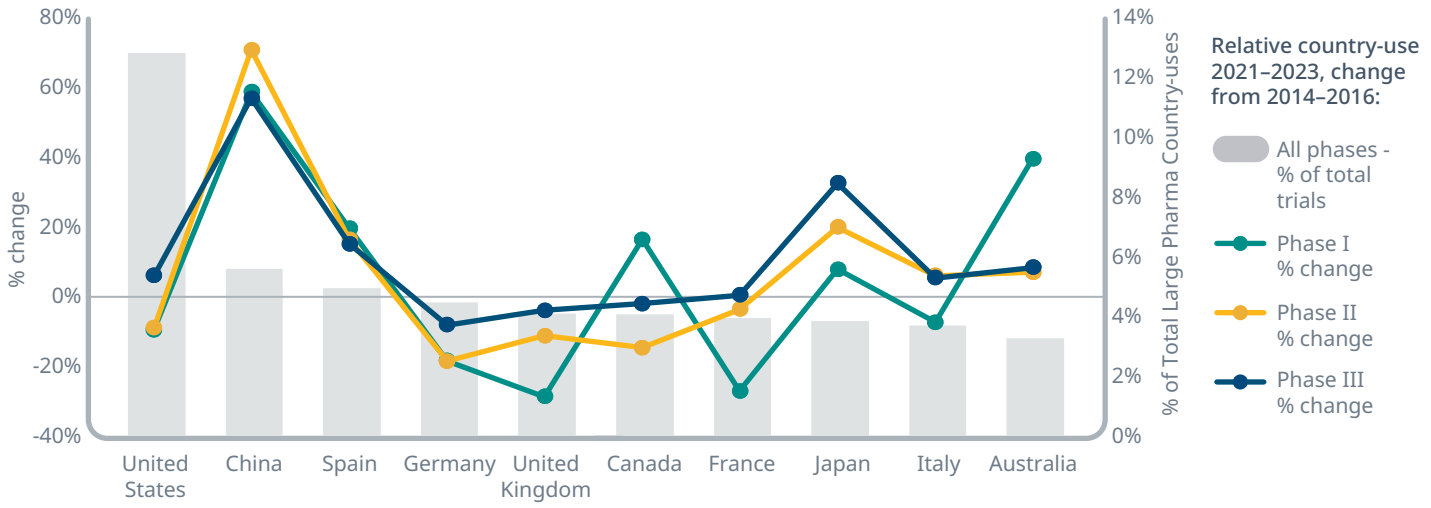


Source: IQVIA Clinical Trial Regulatory Management expert input, IQVIA Institute Jan 2024.

- Evolution of the clinical development regulatory environment has accelerated in recent years, evidenced by the implementation of the Clinical Trial Regulation (CTR) in the EU, MHRA overhaul in response to Brexit, China ICH alignment, and ongoing clinical trial guideline modernization.
- China and EU agencies have been actively focused on improving transparency, but some complexity challenges remain in the EU, resulting in reductions in clinical trial documentation transparency.
- The FDA is still perceived as most focused on flexibly enabling innovative approaches while China, the UK and the EU have increased guidance and openness to innovative approaches with fast-track programs and acceptance of novel trial design.
- China aims to harmonize to FDA and EMA guidance as a member of the ICH but is still perceived as less aligned overall, while the EU CTR lays out ambitious harmonization targets, with the potential for capacity related implementation challenges.
- The U.S. is still providing the fastest decision-making while the UK has shown a rapid clearing of trial assessment backlog in the second half of the year after a focused allocation of resources.
- The EU CTR shifts are contributing to delays in some European countries but are showing progress in process simplification.
- Similarly, China is still experiencing NDA delays driven by complexity and clinical site inspection challenges but is perceived as making progress in process simplification, which should help resolve timing issues.

Large companies reprioritizing country use with significant utilization shifts in top 10 countries in the past decade

Exhibit 52: Country utilization as percent of large company interventional trial country-uses



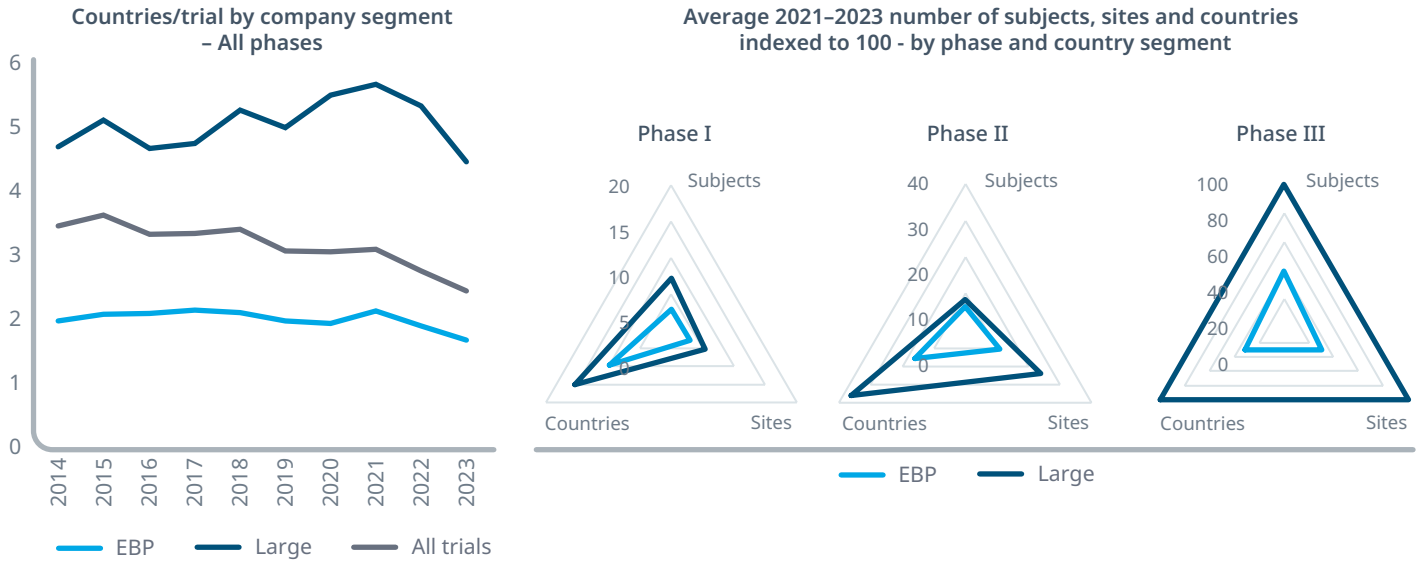
Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Jan 2024.

- Comparison of the top 10 countries by use in large company trials in the past three years to their utilization in 2014–2016 shows significant changes to clinical trial geographic allocation.
- The U.S. has started the largest number of large pharmaceutical trials with about 13% of total trials across all phases in the last three years, and this utilization has remained relatively steady over the past 10 years.
- China, Western European countries, Canada, Japan and Australia round out the top 10 countries most used in large pharmaceutical trials in the past three years, and all have seen moderate to large changes in their relative use.
- China utilization increased the greatest across the analyzed decade, with a more than 50% change in trials across all three phases.
- Spain, Japan, and Australia also saw between 8% and 39% increased relative utilization across phases over the decade.
- Conversely, the UK, Germany, and France had a 29% decrease in relative utilization across all three phases.
- Canada Phase I utilization increased by 16% while Phase II and III utilization decreased slightly.
- Taken together, these results provide evidence that large pharmaceutical companies focus on country, site and subject analytics to optimize geographic trial allocation and productivity.

Notes: Analysis is based on large pharma companies (>$10 Billion annual sales) and their clinical trial starts, highlighting the countries which are included in studies and comparing the most recent three years to the 2014–2016 period. Countries shown are the top 10 countries included across large companies. Trials were industry sponsored and interventional.

Emerging biopharma trials have smaller subject, site and country footprint than large pharmaceutical trials across all phases

Exhibit 53: Average numbers of countries, sites, subjects in Phase I to III trials by company size, 2014–2023



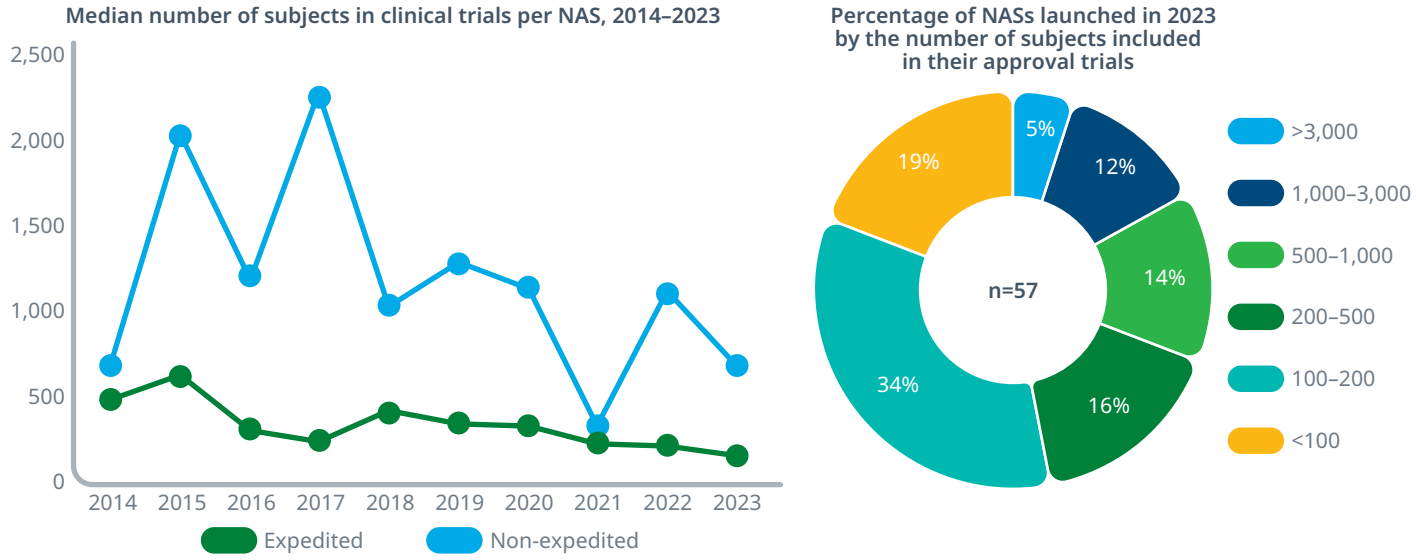
Source: Citeline Trialtrove, IQVIA Institute, Jan 2024.

- The average number of countries used per trial has dropped by 5% for large and 15% for EBP companies over the past decade and across the decade; EBPs use fewer countries per trial than large pharmaceutical companies.
- The total country/trial for all segments of the pipeline has decreased faster (30%) than for either customer segment as a function of the increasing number of EBP trials in the pipeline.
- EBPs have smaller subject, site and country "footprints" than large pharmaceutical companies across all three phases.
- The distinct EBP and large pharma subject, site, country "footprints" also demonstrate a linkage between number of subjects in a trial and the number of countries used.
- Whether due to differences in therapeutic mix, as a necessity due to funding constraints between company types, or as a strategic decision to improve productivity, the increasing proportion of EBPs in the pipeline running trials with fewer subjects, sites and countries is likely contributing to the industry pipeline productivity gains.

Notes: Trials were industry sponsored and interventional. Diagnostics, behavioral therapies, supplements, devices, and medical procedures were excluded. Substantial lags have been noted in the reporting of numbers of subjects, sites, and countries which all rely on site selection, startup, and recruitment and early trial information may not reflect the full extent of the effort required. Therefore, subjects, sites, and countries have been adjusted in the most recent year (2023) based on historic observations of this data latency. The most recent year is subject to change in subsequent periods. The Index of the average number of subjects, sites and countries is based on the largest values in the analysis which are set to 100. Value of 100 for subjects is 2162, 115 for sites and 12 for countries. Large companies are defined as those >$10 Billion in annual sales.

For NASs launched in 2023, 83% included fewer than 1,000 subjects in trials assessed by FDA for approval

Exhibit 54: Number of subjects included in U.S. novel active substance (NASs) approval trials by review status and type



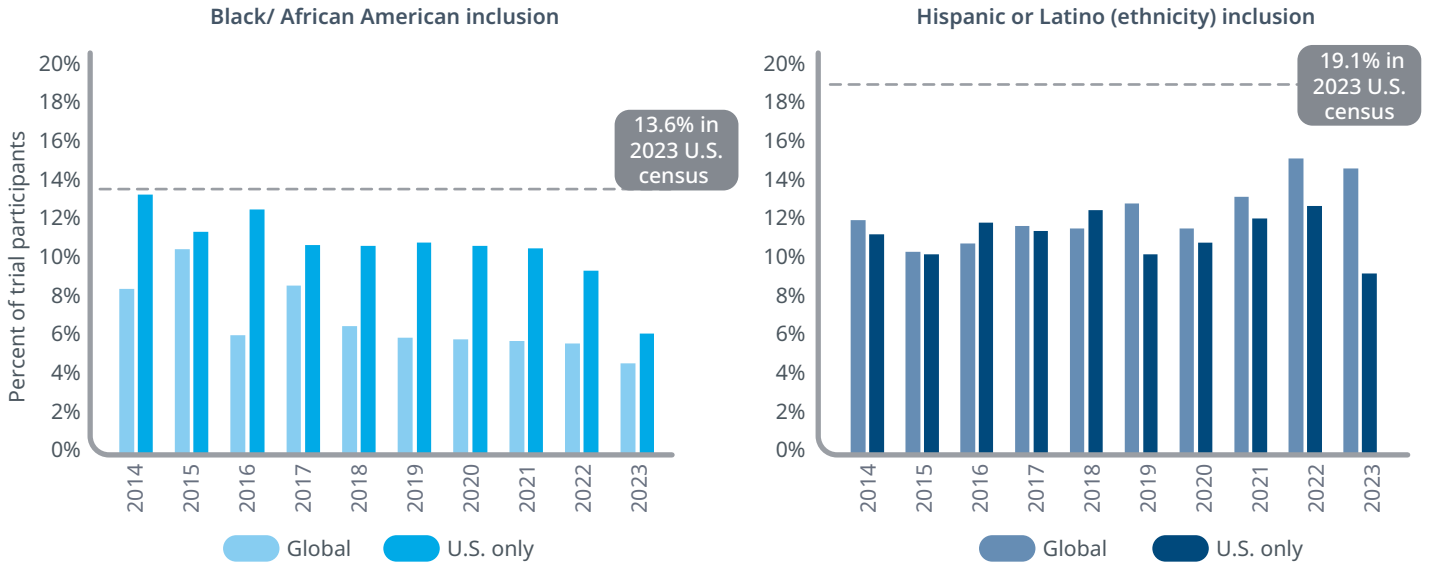
Source: IQVIA Institute, Jan 2024.

- The median number of patients enrolled in approval trials for 2023 launches with some form of expedited review was 22% that of trials for non-expedited launches.
- In the last five years, expedited approval trial enrollment has been 32% lower than for approval trials for non-expedited launches.
- Also in the last five years, the average median enrollment for approval trials for expedited launches has dropped by 52% and 42% for non-expedited launches, indicating that approval trial enrollment numbers are declining overall.
- More than half (53%) of the approval trials for 2023 NAS launches have less than 200 subjects enrolled, and more than three quarters (83%) enrolled fewer than 1,000 subjects.
- There are multiple drivers of the ongoing decline in the number of subjects used by FDA for approval of NAS launches, including the mix of drugs receiving some form of expedited review, and correlated with the pattern that emerging biopharma companies (EBPs) average smaller study enrollment (Exhibits 10, 53).

Notes: Expedited review includes accelerated approval, priority review, breakthrough therapy, and fast track designations, emergency use authorizations; orphan drug designation is not included as an expedited review but noted as it correlates with smaller numbers of trial subjects.

Black/African American and Hispanic patient clinical trial representation dropped over the past decade

Exhibit 55: Phase II and III racial and ethnic inclusion indexed to U.S. demographics, 2014–2023



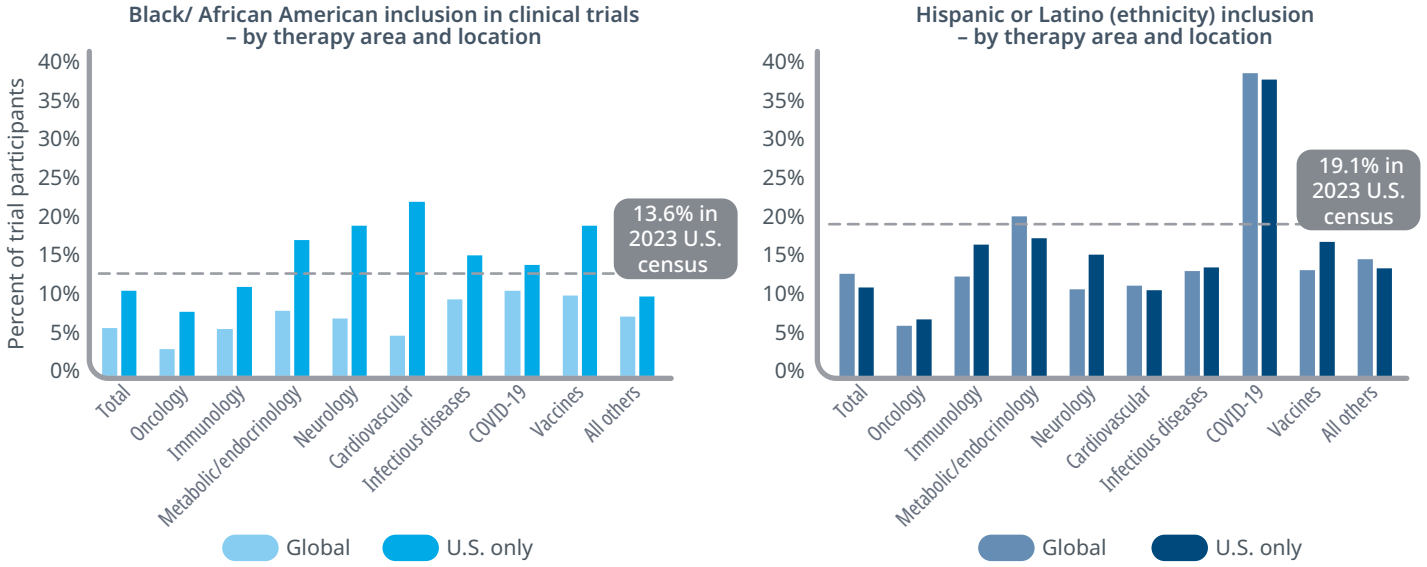
Source: U.S. Census Bureau, 2023; AACT Database, Dec 2023; IQVIA Institute analysis, Jan 2024.

- Sponsors and the FDA are increasingly focused on improving diversity representation and the reporting of these results in clinical trials.
- Despite these efforts, Black/African American and Hispanic patient inclusion continue to fail to reach U.S. demographic levels on average across interventional trials in the past decade.[7–9]
- As racial and ethnicity demographics vary across countries, difficulties remain in finding true representativeness of the U.S population among global sites, especially for Black/African Americans, but even with U.S. only studies, studies fail to achieve representativeness.
- Trial participation for Black/African Americans and Hispanic or Latino in U.S. only or global sites fall short on average of the 2023 U.S. demographics of 13.6% and 19.1%, respectively.
- Black/African American participation has been stable in the past few years, with a notable drop of 4% in U.S.-only sites trial participation between 2021 (11%) and 2023 (6%).
- Similarly, Hispanic inclusiveness has varied in the past decade and never reached U.S. demographic levels among both U.S only and global sites. Hispanic participation reached its lowest point for the past decade in 2023, representing 9% in Phase II and III trials with U.S-only sites.
- In August 2023, the FDA drafted guidance calling on sponsors to complete data collection of underrepresented populations in post-market data collection should it be missing from pre-market data. The effects of this recent effort to improve diverse representation in clinical trials remains to be seen in the years to come.[10]

Notes: Includes all interventional Phase II and III trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov starting after 2009 and completing between the start of 2014 and the end of 2023. Only trials with racial or ethnic data collected were included in calculation of Black/African American or Hispanic patient inclusion, respectively. Analysis includes 4,947 trials over the time period. Average U.S. Black / African American representation is 13.6% and U.S Hispanic or Latino representation is 19.1%.

Clinical trial participation varies widely across therapeutic areas in U.S. vs. global trials

Exhibit 56: Phase II and III Black/African American and Hispanic patient inclusion by therapeutic area and geography, 2019–2023



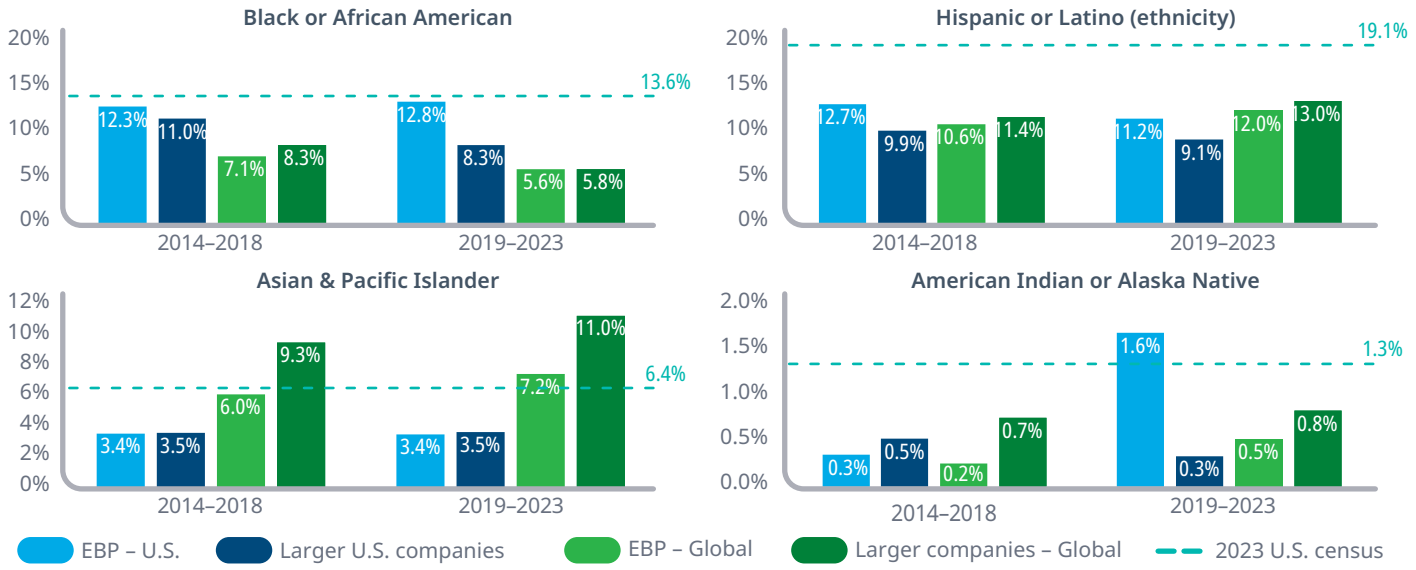
Source: U.S. Census Bureau, 2023; AACT Database, Dec 2023; IQVIA Institute analysis, Jan 2024.

- Black/African American and Hispanic inclusion varied in their top therapeutic areas; both were generally higher across all therapeutic areas in trials which were recruited exclusively in the U.S., and both saw the lowest levels of inclusion in oncology.
- Black/African American inclusion ranged from 22% (1.6 times higher than U.S. demographic) of patients in U.S.-only run cardiovascular trials to 3% (20% of the U.S. demographic levels) of globally run oncology trials.
- Hispanic inclusion ranged from 37% (1.9 times higher than the U.S. Hispanic demographic) in U.S.-run COVID-19 studies to 6% (31% of U.S. demographic) of globally run oncology trials.
- Notably, even in U.S. only site trials, Black/African American and Hispanic inclusion in oncology only reached 58% and 37% of the U.S. demographic levels, respectively.
- Poor inclusivity in oncology, which averages 36% of trial starts over the past five years, has an outsized impact on overall rates of inclusivity.
- The inclusivity disparities in the largest clinical development segments mirror some of the healthcare disparities in the U.S. overall and provide directed improvement opportunities for stakeholders.[11,12]
- In a November 2023 report, the FDA found that 87% of studies between April 2022 and April 2023 had a completed inclusivity plan, but only 6% of those contained required and acceptable diversity information, consistent with this analysis.[13]

Notes: Includes all interventional Phase II and III trials with industry involvement and any U.S. sites listed on ClinicalTrials.gov starting after 2009 and completing between the start of 2019 and the end of 2022. Only trials with racial or ethnic data collected were included in calculation of Black/African American or Hispanic patient inclusion, respectively.

Larger company sponsors are achieving worse representation in trials compared to emerging biopharma sponsors

Exhibit 57: Phase II and III racial and ethnic patient inclusion by company size and geography, 2014–2023



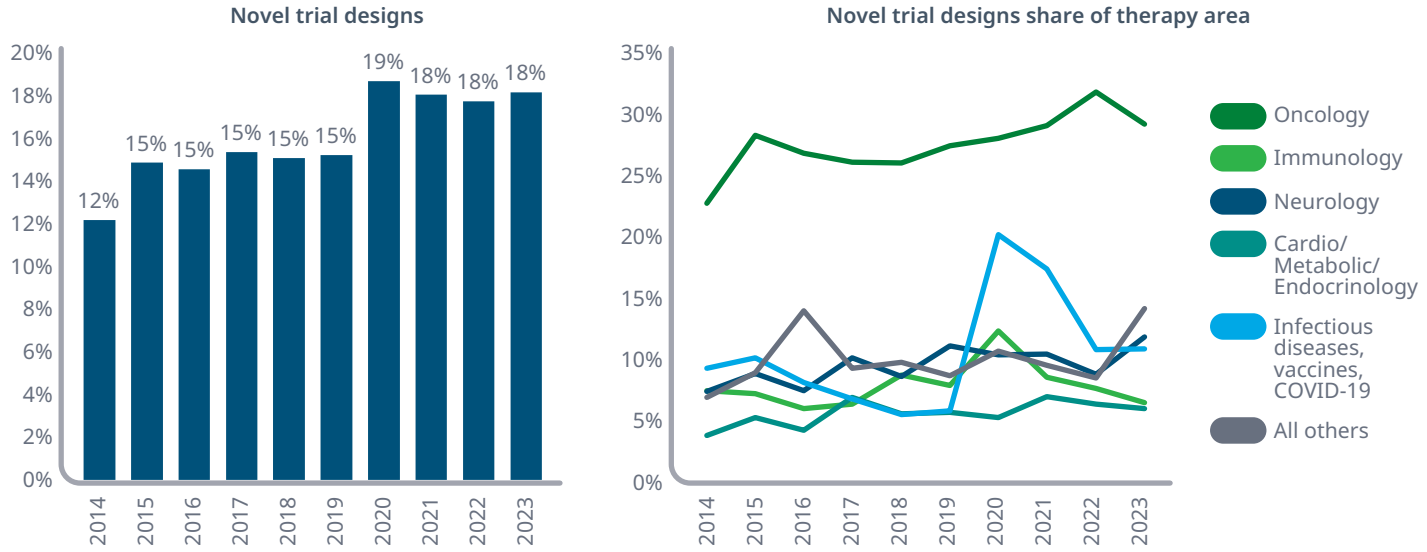
Source: U.S. Census Bureau, 2023; AACT Database, Dec 2023; IQVIA Institute analysis, Jan 2024.

- In the past five years, larger companies have generally achieved worse racial and ethnic representation than emerging biopharma companies (EBPs) when sponsoring trials of U.S. only sites –ranging between 1% to 10% of difference from U.S. demographics.
- Black or African American representation in trials decreased in the recent period, with EBP and larger company sponsored U.S.-only sites both worse in the more recent period.
- For the past decade, global site trials have increased their over-representation of Asians and Pacific Islanders — by almost 3% during the 2014-2018 period and almost 5% in the 2019–2023 period.
- With EBPs responsible for two-thirds of the R&D pipeline during the past decade and with their share continuing to grow, their imprint on racial and ethnicity representation in trials will only increase.

Notes: Emerging biopharma (EBP) companies are defined as those with either R&D spend <$200 million or prescription sales up to $500 million. Companies with any active pipeline since 2014 were included. Large companies are those with global prescription sales exceeding $10 billion in the calendar year.

Novel trial designs have averaged 18% of trials since 2020, led by oncology with over 29% novel designs

Exhibit 58: Novel trial design starts by year and therapy area, 2014–2023



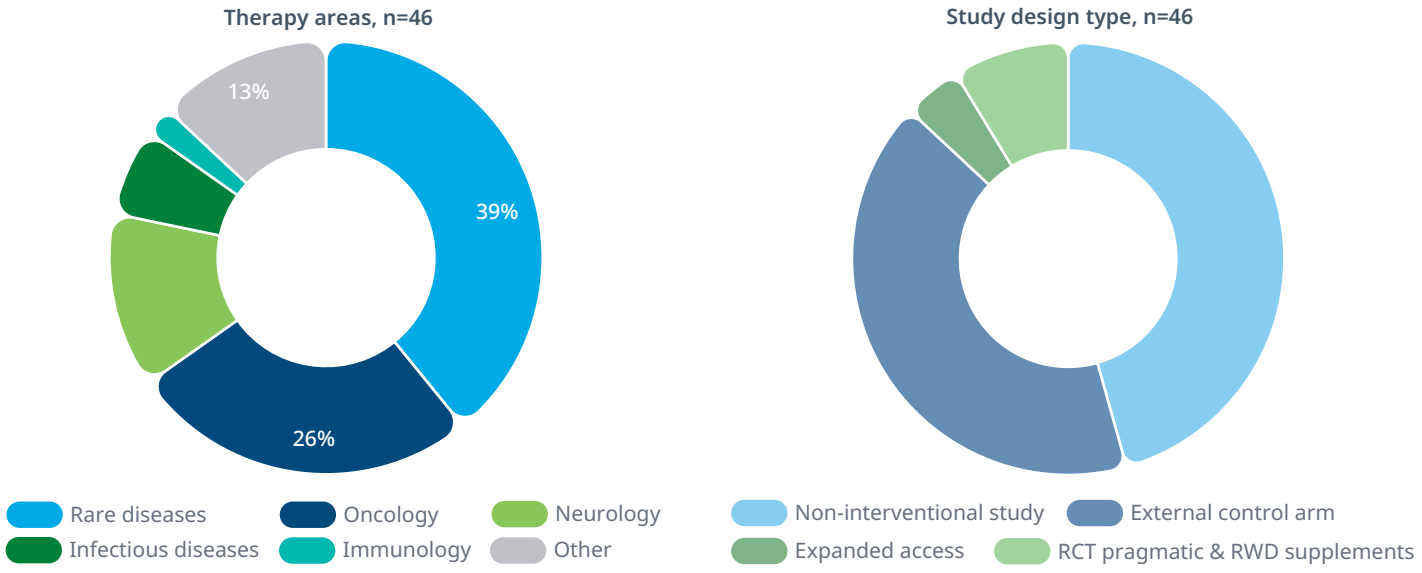
Source: Citeline Trialtrove, IQVIA Institute, Jan 2024.

- Novel trial designs, including umbrella, basket, master, and adaptive protocols, form a foundational part of the clinical trial pipeline and have been included in 18% of trials since 2021.
- Novel trial design utilization is highest in oncology trials, accounting for 29% of these trials in 2023, down from a peak of 32% in 2022 but up from 13% in 2014.
- Infectious disease saw a spike in novel trial design use through the pandemic as COVID-19 trials widely leveraged master protocols and adaptive structures to enable parallel processing, accelerate program data collection, and improve decision-making, but have returned to and remained steady at pre-pandemic levels since 2022.
- Neurology trials have also been increasingly using novel trial design strategies since 2014, with strategies employed in 12% of the 2023 neurology trials.
- It is likely that increasing use of novel trial designs will continue to contribute to industry productivity as NTDs build a foundation across critical therapy areas, increasing knowledge, failing faster, and consistent with faster development timelines for clinical programs that include combined phases often enabled by NTD.

Notes: Novel trial designs include umbrella, basket, adaptive, master protocol, dose escalation + dose expansion studies using a range of keyword strings. Share based on industry interventional studies plus novel trial design studies from non-industry sponsors. Most non-industry sponsors are understood to have received some degree of funding from industry in these trials. Novel trial design share is based on all industry/interventional trials plus any novel trial design studies. In the studies analyzed, non-industry novel trial design studies represented 16% of these studies.

Both sponsors and the FDA are increasing their focus and incorporation of RWE for regulatory decision-making

Exhibit 59: FDA approvals based on real-world evidence (RWE), 2014–2023



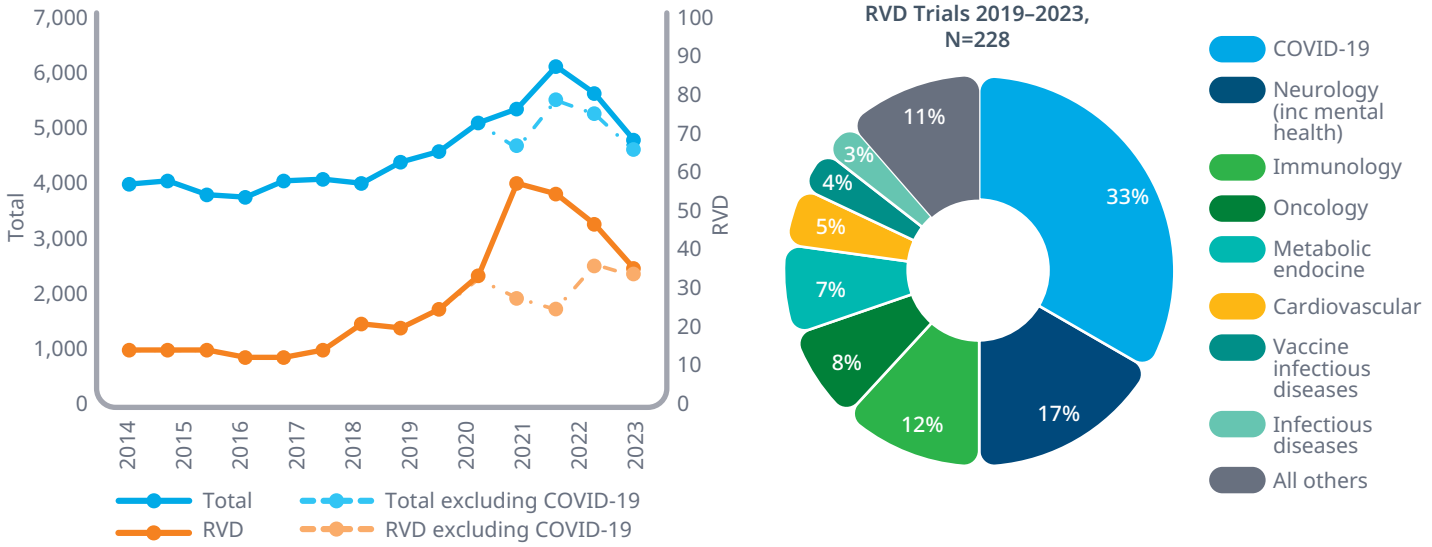
Source: IQVIA Institute, Jan 2024.

- Real-world evidence (RWE) and real-world data (RWD) represent significant opportunities to contribute to improved clinical development program productivity, including use in regulatory approval applications.
- It is understood that a large percentage of submissions include RWE components in the information provided to the FDA[14], but many fewer studies are explicitly noted by the FDA as a basis for approval.
- Over the past decade, RWE has been publicly cited in approval letters as a basis for approval by FDA for new approvals or expanded use of existing drugs 46 times.
- Approvals citing RWE have most often been in rare diseases, oncology and neurology studies, and have non-interventional designs or act as external controls.
- The FDA has issued multiple guidelines on the use of RWD/RWE in clinical development since the release of the 21st Century Cures Act (2016), including multiple publications in 2023 on use in medical device development, and finalization of 2021 guidance on use in medical product development and further refinement of data standards for use of RWD as RWE.
- Future expanded utilization of RWE, decision-making transparency, and pilot program agency partnerships are expected following the September 2022 guidance on submissions of RWE and RWD[15] and the October 2022 FDA announcement of the Advancing RWE Program in fulfillment of PDUFA VII obligations.[16]

Notes: Collected from public sources relating to the approval trials for medicines. Data collected under a treatment IND or expanded access protocol has been considered a form of RWE by the FDA, such as in rare disease settings where there is little chance of a prospective trial. RWE approvals shown here include those granted after approval (e.g., carglumic acid 2010 RWE but drug was a 2006 launch). Analysis includes some double counting where a drug may have had more than one type.

Trials which are remote, virtual or decentralized have been increasing in line with the industry trial starts but focus in different diseases

Exhibit 60: Trial starts for all trials and remote, virtual or decentralized trials (RVD), 2014–2023



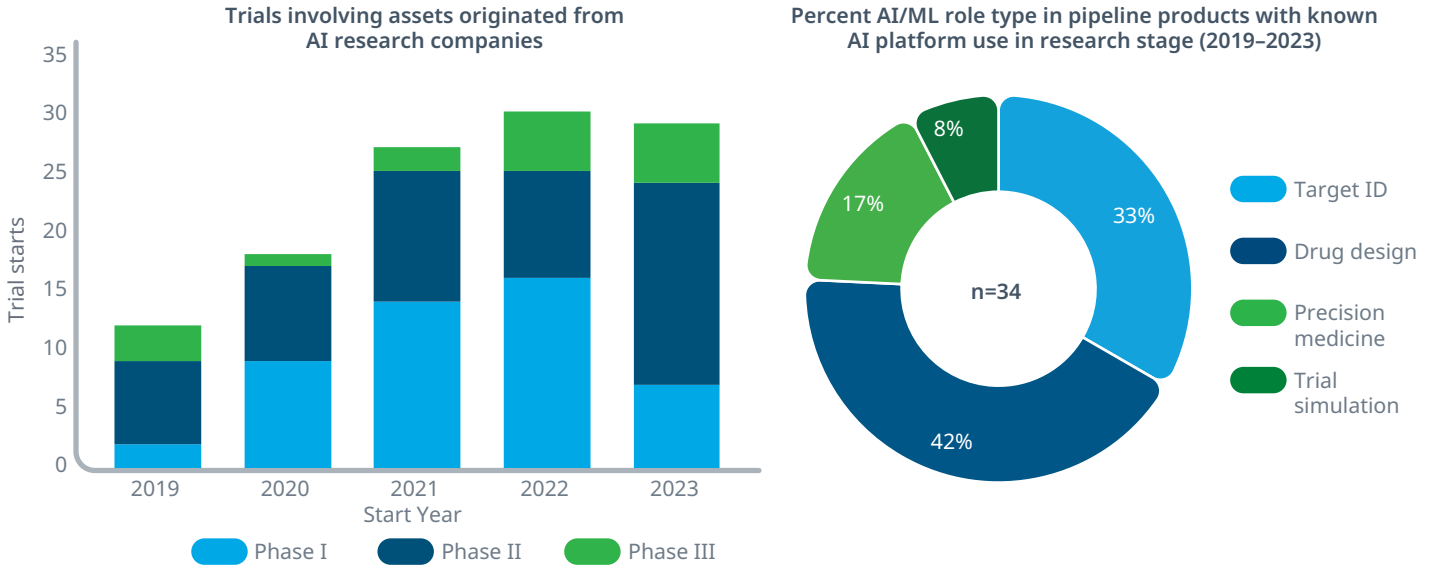
Source: Citeline Trialtrove, IQVIA Institute, Jan 2024.

- The relative discoverable use of remote, virtual or decentralized methods in clinical trials continued to dip in 2023 to resume modest pre-COVID-19 growth trajectory.
- Early 2020 saw a very sharp increase in reported decentralized methods that mirrored a sharp increase in total trial activity driven by COVID-19 therapy and vaccine development.
- Removal of COVID-19 trials from the analysis shows that trials with decentralized methodologies dropped in 2020 and 2021 relative to total non-COVID-19 trials, suggesting that COVID-19 trials may have taken up all decentralized trial "capacity."
- Non-COVID decentralized trial use rebounded in 2022 and 2023, giving some indication that though detected at relatively low levels, decentralized trials may have become more established resulting from a critical need and rapid implementation during the pandemic.
- RVD trials run between 2019 and 2023 are most heavily focused on COVID-19 followed by neurology and immunology.

Notes: Trials which have a number of decentralized features often don't disclose those in trial registry information. Analysis includes industry and non-industry, and interventional and non-interventional trials to enable identification of utilization trends.

Maturation of AI drug discovery through the clinical trial pipeline includes launch of repurposed drugs for new uses

Exhibit 61: Impact of artificial intelligence (AI) on industry clinical development pipeline



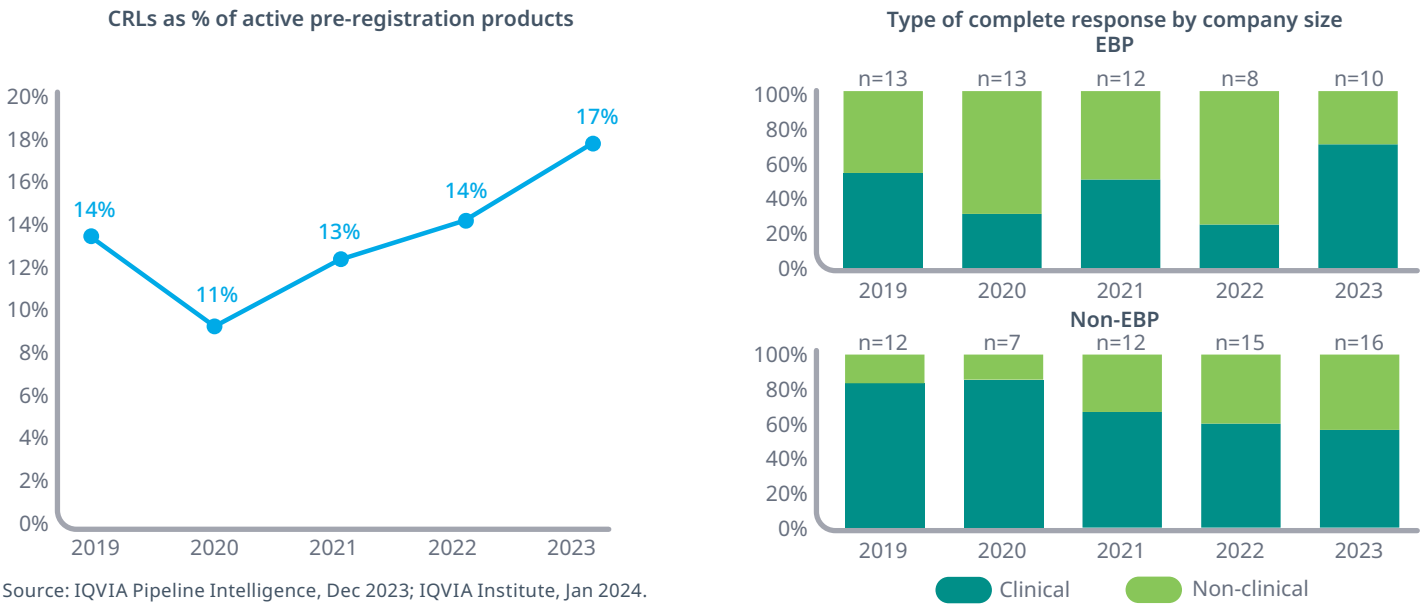
Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Jan 2024.

- Start-up and established healthcare companies are applying AI/ML technology to leverage growing chemical, biological and patient datasets to accelerate and improve drug target and drug selection across the entire drug discovery continuum, with a set of most-used applications emerging in the clinical pipeline.
- The number of trials involving molecules that were discovered and researched by a cohort of AI/ML research focused companies with the use of AI/ML technology has been increasing over the last five years.
- This pipeline of AI/ML-originated molecules shifted to later stage development in 2023, with the number of Phase II studies nearly doubling from the year before.
- AI target selection by interrogating clinical, experimental and 'omics' data to better characterize disease states and identify novel 'druggable' targets has been used in 33% of the AI/ML impacted molecules analyzed.
- Drug design represents the most common use of AI/ML in the analyzed cohort, with 42% of analyzed products optimizing drug design by analyzing complex datasets, including molecule structure, molecular dynamics, genome, and combinatorial drug screening.
- The use of AI/ML to deliver insight from range of patient 'omics,' biometrics and previous trial data to specifically optimize drug discovery through precision patient targeting has been used in 17% of the products in the analyzed cohort.
- Finally, trial simulation using AI/ML technologies on target, drug, and patient datasets is enabling optimized clinical trial design in 8% of the pipeline products analyzed.

Notes: Analysis tracks molecules that were discovered and/or researched by a cohort of companies that are using AI/ML for drug discovery. The analysis of AI/ML companies is not exhaustive, and some AI activities may not be disclosed, as a result, this analysis is directional. Each identified product may have more than one type of AI/ML role included in the analysis. This analysis does not include the use of AI/ML for clinical trial operations optimization including site and patient selection, or histology/pathology or end point analysis. Analysis includes terminated trials.

Applicants are receiving more complete response letters from FDA with an increase in clinically driven responses for EBPs

Exhibit 62: Share of active pre-registration products with complete response letters and types of responses by company segment, 2019–2023



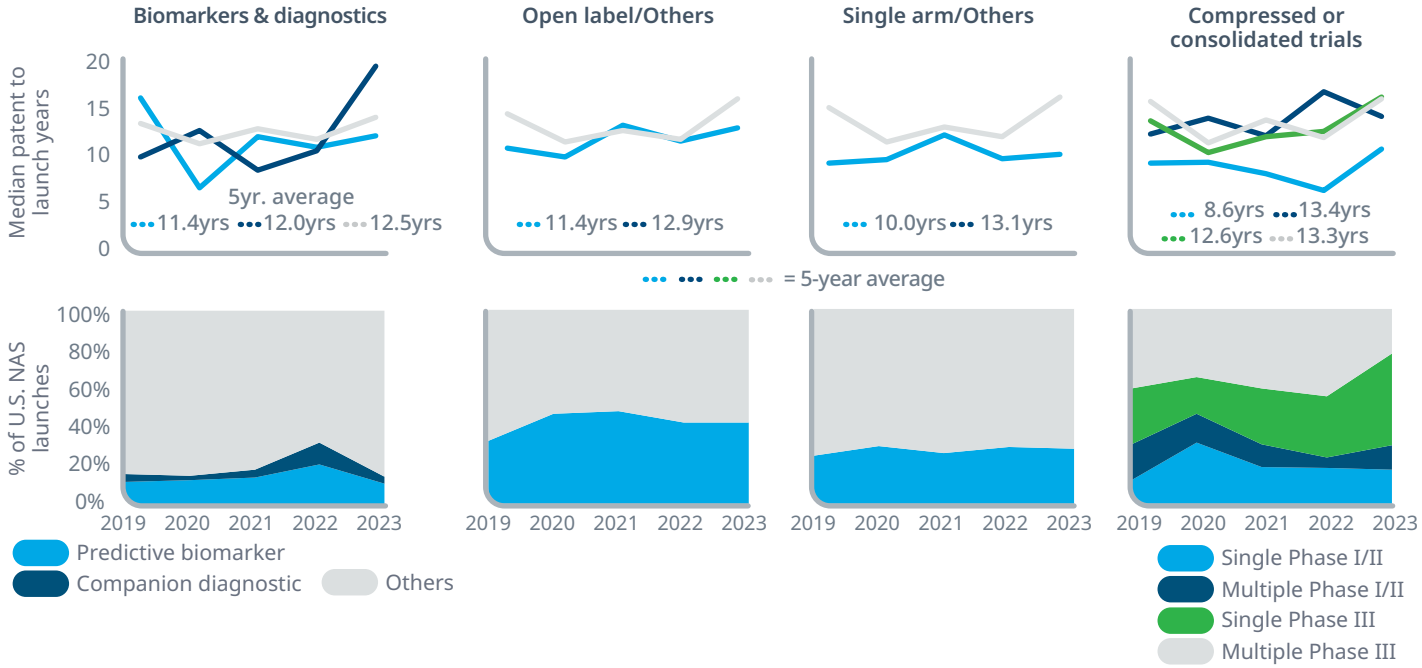
Source: IQVIA Pipeline Intelligence, Dec 2023; IQVIA Institute, Jan 2024.

- The FDA issues complete response letters when it decides it will not approve a drug application and can include reasons such as manufacturing or quality issues or insufficient clinical trial data.
- Industry has been focused on minimizing regulatory setbacks in the form of complete response letters (CRLs), especially for clinical reasons, although overall rates were higher in 2023. Operational or non-clinical reasons for CRLs have been impacting emerging biopharma companies differently than larger firms.
- Emerging biopharma companies received complete response letters at a 38% higher rate than larger companies when comparing to the number of products filed by each with the FDA.
- There were 56 complete response letters received by emerging biopharma, with 54% for non-clinical reasons compared to 62 complete responses letters for larger companies, but only 32% for non-clinical reasons.
- When emerging biopharma companies receive complete response letters for clinical reasons, they are more likely to resubmit than larger companies, as these companies tend to be developing few products and have higher risk with abandoning a product.
- When complete response letters are for non-clinical reasons such as for manufacturing, product quality, or chemistry data, two-thirds of the time these are resubmitted within a short time period to the FDA.

Notes: Company segment when two or more companies are involved is determined by the larger sales segment. Information collated from public sources including FDA and company press releases. May not include complete response letters which were received by companies and not publicly disclosed. A submission may receive complete responses that have both clinical and non-clinical reasons and some responses are double-counted.

Notable aspects of trial programs and design contribute to much shorter development durations

Exhibit 63: U.S. novel active substances launches and time from first patent filing by characteristics of approval, 2019–2023



Source: IQVIA Institute, Jan 2024.

- As sponsors work to improve R&D productivity, benchmarks for development timelines provide useful context.
- For drugs with a compressed or consolidated trial sequence — being ultimately approved based on one or more earlier phase trials — development durations have averaged over four years less than those with more traditional trial sequences.
- As it may be possible to recruit trial subjects and generate results more quickly in a single-arm trial, and it has been common for breakthroughs with greater unmet needs to allow approval based on single trials, these single-arm trials as the basis for approval are three years earlier than other approvals.
- While drugs with predictive biomarkers or launched with a companion diagnostic are fewer than 20% of NASs in most years, their development timelines average up to a year faster than other drugs.

Notes: A novel active substance (NAS) is a new molecular or biologic entity or combination where at least one element is new; Includes NASs launched in the United States 2019-2023 regardless of the timing of FDA approval. Duration calculations include the first patent or first human trial, whichever is earlier, and count duration until confirmed launch in the United States. Duration calculations are expressed as medians or the relevant segments.

Notes on sources

THIS REPORT IS BASED ON THE IQVIA SERVICES DETAILED BELOW

ARK PIPELINE INTELLIGENCE is a drug pipeline database containing up-to-date R&D information on over 40,000 drugs, and over 9,000 in active development worldwide. The database captures the full process of R&D, covering activity from discovery stage through preclinical and clinical development, to approval and launch. The database is being replaced with IQVIA Pipeline Link which is available today but was not utilized for this study.

ARK PATENT INTELLIGENCE™ is a database of biopharmaceutical patents or equivalents in over 130 countries and including over 3,000 molecules. Research covers approved patent extensions in 51 countries, and covers all types of patents including product, process, method of use and others .

IQVIA™ PHARMA DEALS is a comprehensive life science deals and alliances database that leverages worldwide information sources to deliver the latest intelligence in deals and alliances.

THIRD-PARTY INFORMATION:

CITELINE'S TRIALTROVE provides intelligence about the drug development pipeline and information on clinical trials globally. Citeline reports that Trialtrove uses over 40,000 sources including ones in the public domain and is supported by experienced industry analysts. The database includes extracted information including protocol details, as well as additional industry-relevant search terms such as its proprietary patient segments, trial outcomes and biomarker tags. It includes information on trial design, eligibility criteria, endpoints, sites, sponsors as well as anticipated and actual start and end dates as available. These attributes have been leveraged extensively in the IQVIA Clinical Productivity Index. For more information on Trialtrove see www.pharmaintelligence.informa.com/clinical-trial-data

BIOWORLD is a suite of news services run by Clarivate which includes tracking and segmentation of biopharmaceutical funding deals including venture capital, IPO and follow-on financing and other public financing.

Methodologies

SUCCESS RATES

Using IQVIA Pipeline Intelligence, which includes event dates for a comprehensive range of drug development stages where disclosed or able to be determined by editorial staff, phase start dates were tracked for each product. A phase was considered successful if any subsequent phase has a later phase start date. In the absence of a subsequent phase start, the highest date for a negative event such as discontinuation, suspension, withdrawn by applicant, or inactive for greater than three years was examined. Analysis was conducted across all indications and considers success or failure at the drug level and so did not track a specific indication for each drug but rather measured the success of the overall program.

More than 33,000 distinct drugs were examined for over 130,000 potential phase transitions for events from 1977 to the present. We then limited to products where the phase transitions completed between 2010 and 2023, with valid information regarding phase transitions, either successful or failed, which includes more than 9,000 distinct drugs and over 13,000 phase transitions.

We consider the earliest date a drug entered each phase. We consider the latest date for negative event outcomes. Negative outcomes include discontinued, suspended and withdrawn which are noted in the data collection when the sponsor discloses it. Negative events also include inactivity which is determined when there is no verified activity for three years. Inactive records are assigned to the year inactivity was determined (last time record was active plus three years).

COMPLEXITY METRICS

Clinical trial data included in the complexity metrics — trial start and end dates, country locations, number of clinical sites, actual or target number of subjects, endpoints, and inclusion/exclusion criteria — rely on company reported information about ongoing or planned clinical trials. Substantial lags have been noted in the reporting of numbers of subjects, sites, and countries which all rely on site selection, startup, and recruitment and early trial information may not reflect the full extent of the effort required.

Historic evaluations of different year-end editions of this data indicate variation in the individual measures included in the complexity metric in the most recent year of data. In particular, the number of sites, countries, and subjects have shown significant variability in the numbers reported from one year to the next. Comparing across the year-end editions for 2020–2022, complexity metrics for average number of countries across all phases increased 13% in the latest year, sites increased 29%, and subjects increased 33%. These variations had an impact on overall complexity and productivity, increasing complexity in the most recently published year by 15% and decreasing productivity 6%.

Therefore, subjects, sites, and countries have been adjusted in the most recent year (2023) based on historic observations of this data latency. The most recent year is subject to change in subsequent periods.

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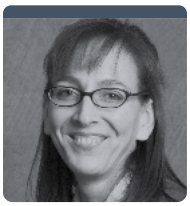
About the authors

MURRAY AITKEN
Executive Director,
IQVIA Institute for Human Data Science

Murray Aitken is Executive Director, IQVIA Institute for Human Data Science, which provides policy setters and decisionmakers in the global health sector with objective insights into healthcare dynamics. He led the IMS Institute for Healthcare Informatics, now the IQVIA Institute, since its inception in January 2011. Murray previously was Senior Vice President, Healthcare Insight, leading IMS Health's thought leadership initiatives worldwide. Before that, he served as Senior Vice President, Corporate Strategy, from 2004 to 2007. Murray joined IMS Health in 2001 with responsibility for developing the company's consulting and services businesses. Prior to IMS Health, Murray had a 14-year career with McKinsey & Company, where he was a leader in the Pharmaceutical and Medical Products practice from 1997 to 2001. Murray writes and speaks regularly on the challenges facing the healthcare industry. He is editor of Health IQ, a publication focused on the value of information in advancing evidence-based healthcare, and also serves on the editorial advisory board of Pharmaceutical Executive. Murray holds a Master of Commerce degree from the University of Auckland in New Zealand, and received an M.B.A. degree with distinction from Harvard University.



NICOLE CONNELLY
Research Director,
IQVIA Institute for Human Data Science

Nicole serves as Research Director for the IQVIA Institute for Human Data Science, leading Institute research focused on global pharmaceutical R&D-related topics. In this work, she partners with team members, IQVIA experts, and industry thought leaders to bring insights on R&D performance and ongoing innovation. Prior to joining the Institute in late 2021, she was Senior Director of R&D Strategy at IQVIA, where she partnered with the organization's leaders to frame corporate and therapeutic growth strategies. She also worked in the IQVIA Consulting organization from 2008 to 2014, leading projects with pharmaceutical and biotech clients and helping to optimize cross-functional drug development solutions. Before coming to IQVIA, Nicole worked in R&D organizational effectiveness at Pfizer, and began her career in 2008 in the Pharmaceutical and Medical Product practice at McKinsey & Company. Nicole holds a Ph.D. in Microbiology from Duke University and a B.S. in Biology from the State University of New York at Fredonia.

MICHAEL KLEINROCK
Research Director,
IQVIA Institute for Human Data Science

Michael Kleinrock serves as Research Director for the IQVIA Institute for Human Data Science, setting the research agenda for the Institute, leading the development of reports and projects focused on the current and future role of human data science in healthcare in the United States and globally. Kleinrock leads the research development included in Institute reports published throughout the year. The research is focused on advancing the understanding of healthcare and the complex systems and markets around the world that deliver it. Throughout his tenure at IMS Health, which began in 1999, he has held roles in customer service, marketing, product management, and in 2006 joined the Market Insights team, which is now the IQVIA Institute for Human Data Science. He holds a B.A. degree in History and Political Science from the University of Essex, Colchester, UK, and an M.A. in Journalism and Radio Production from Goldsmiths College, University of London, UK.

JAMIE PRITCHETT
Associate Thought Leadership Director, IQVIA Institute for Human Data Science

Jamie is a Thought Leadership Manager for the IQVIA Institute, managing aspects of IQVIA Institute research projects and conducting research and analysis within global healthcare. Prior to joining IQVIA in 2021, he held positions with the North Carolina Department of Health and Human Services and the Duke Human Vaccine Institute, where he developed skills in understanding and addressing the array of physical, environmental and social contributors to individual health. Jamie uses his experience in public health, health communication, and drug development and research to understand current trends in healthcare and the life sciences industry.
He holds a Bachelor of Science in Animal Science and Zoology and a Master of Toxicology from North Carolina State University.

About the Institute

The IQVIA Institute for Human Data Science contributes to the advancement of human health globally through timely research, insightful analysis and scientific expertise applied to granular non-identified patient-level data.

Fulfilling an essential need within healthcare, the Institute delivers objective, relevant insights and research that accelerate understanding and innovation critical to sound decision making and improved human outcomes. With access to IQVIA's institutional knowledge, advanced analytics, technology and unparalleled data the Institute works in tandem with a broad set of healthcare stakeholders to drive a research agenda focused on Human Data Science including government agencies, academic institutions, the life sciences industry, and payers.

Research agenda

The research agenda for the Institute centers on five areas considered vital to contributing to the advancement of human health globally:

- Improving decision-making across health systems through the effective use of advanced analytics and methodologies applied to timely, relevant data.
- Addressing opportunities to improve clinical development productivity focused on innovative treatments that advance healthcare globally.
- Optimizing the performance of health systems by focusing on patient centricity, precision medicine and better understanding disease causes, treatment consequences and measures to improve quality and cost of healthcare delivered to patients.
- Understanding the future role for biopharmaceuticals in human health, market dynamics, and implications for manufacturers, public and private payers, providers, patients, pharmacists and distributors.
- Researching the role of technology in health system products, processes and delivery systems and the business and policy systems that drive innovation.

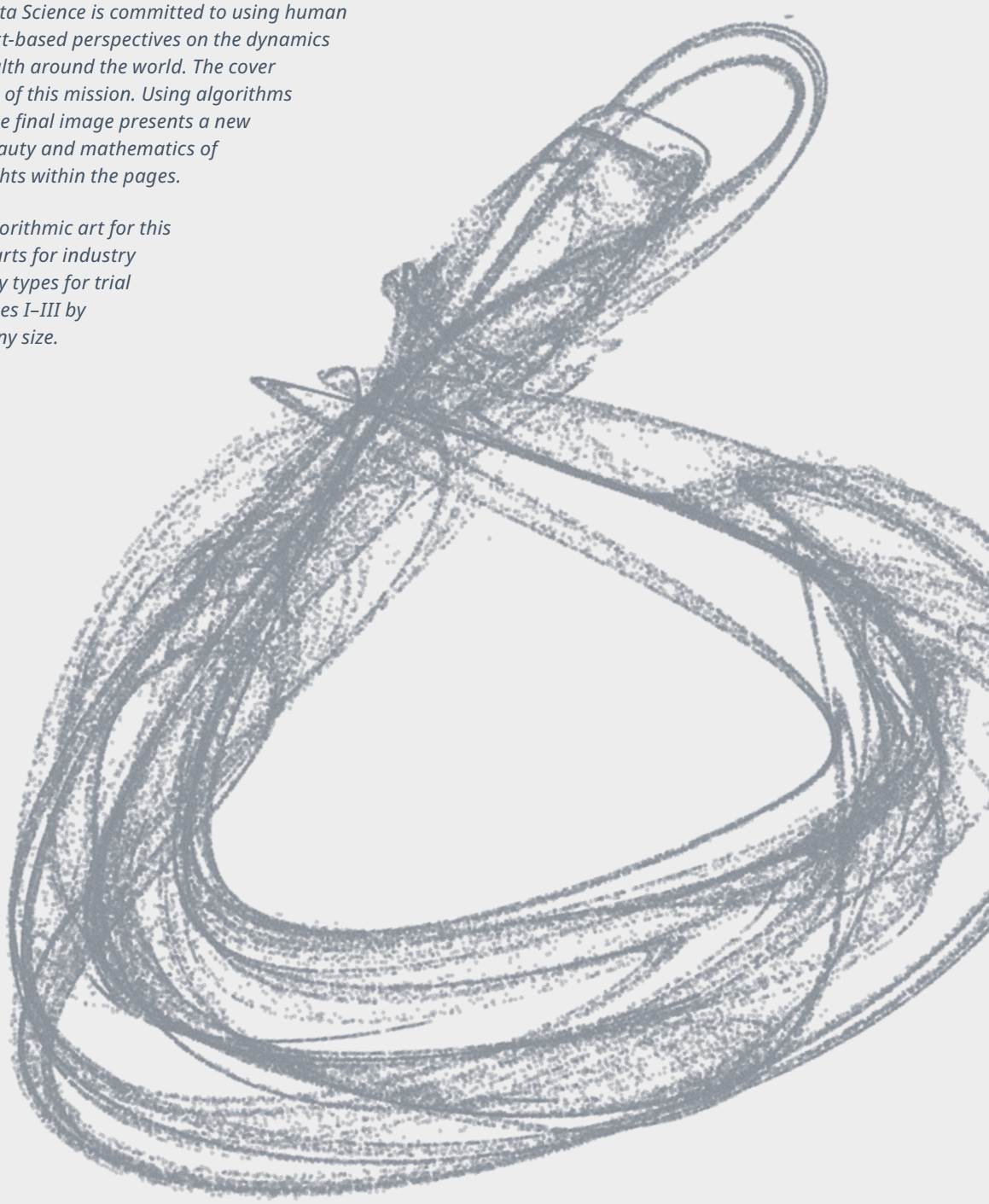
Guiding principles

The Institute operates from a set of guiding principles:

- Healthcare solutions of the future require fact based scientific evidence, expert analysis of information, technology, ingenuity and a focus on individuals.
- Rigorous analysis must be applied to vast amounts of timely, high quality and relevant data to provide value and move healthcare forward.
- Collaboration across all stakeholders in the public and private sectors is critical to advancing healthcare solutions.
- Insights gained from information and analysis should be made widely available to healthcare stakeholders.
- Protecting individual privacy is essential, so research will be based on the use of non-identified patient information and provider information will be aggregated.
- Information will be used responsibly to advance research, inform discourse, achieve better healthcare and improve the health of all people.

The IQVIA Institute for Human Data Science is committed to using human data science to provide timely, fact-based perspectives on the dynamics of health systems and human health around the world. The cover artwork is a visual representation of this mission. Using algorithms and data from the report itself, the final image presents a new perspective on the complexity, beauty and mathematics of human data science and the insights within the pages.

The data used to generate the algorithmic art for this report is based on clinical trial starts for industry sponsors with interventional study types for trial starts between 2014-2023 in Phases I–III by therapy area and sponsor company size.



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CONTACT US
100 IMS Drive
Parsippany, NJ 07054
United States
info@iqviainstitute.org
iqviainstitute.org