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Seeds of change
Measuring the return from
pharmaceutical innovation 2020

May 2021

Contents

Deloitte Centre *for*
Health Solutions

GlobalData.

Foreword

Welcome to *Seeds of change*, the latest in our series of reports from the Centre for Health Solutions exploring the performance of the biopharmaceutical (biopharma) industry in generating returns from investments in innovative new therapies. This year's report is a transition report, as we move from analysing two separate cohorts of companies to focusing on a single combined cohort. This reflects the fact that the performances of our two cohorts have converged and also our desire to undertake a more granular analysis.

Between 2010 and 2020 our *Measuring the return from pharmaceutical innovation* series tracked the return on investment that an original cohort of 12 leading global biopharma companies might expect to achieve from their late-stage pipeline. For the past seven years we also tracked the performance of an extension cohort of four more specialised biopharma companies, using the same comprehensive and consistent methodology. The companies in the extension cohort can no longer be differentiated in terms of scale or even pharmaceutical R&D spending from the companies in the original cohort. In addition, in 2020, for the first time, two of the companies merged (reducing the extension cohort to just three). This year's report is therefore a transition report that considers the performance of the two cohorts as a single combined cohort.

Overall, the combined cohort has seen a decade-long decline in projected R&D productivity, reflecting the challenges faced by the industry more widely. However, for the first time since 2014, the average IRR has had an uptick from the previous year, suggesting signs of a potential reversal in the declining trend. While some companies have seen a few impressive peak sales projections, they are still facing the rising costs of conducting clinical trials as well as longer cycle times. In recent years, we have seen the development of some novel trial designs and improvements in efficiency through digitalisation of drug discovery and development, but until recently their adoption was experimental and not at scale. The COVID-19 pandemic has changed this, with the 'need for speed' becoming all-encompassing alongside the realisation that development cycle times had to be reduced and new ways of working adopted.

The legacy of these 'seeds of change' is likely to be faster drug development, but only if the collaboration between organisations and new regulatory paradigms that emerged during the pandemic can become fully embedded; and the use of digital and other transformative approaches to expedite drug development are adopted at scale. Improving drug discovery and development will also require companies to attract and retain people with relevant clinical, scientific and data science/data ethics skills and talent and have AI-friendly and tech-savvy leaders, willing to embrace new business and operating models.

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2020 results for our combined cohort of 15 biopharma companies

R&D returns have seen an **uptick** across the companies analysed for the **first time since 2014**

2013
6.4%

2014
7.2%

2015
6.1%

2016
5.5%

2017
5.3%

2018
3.5%
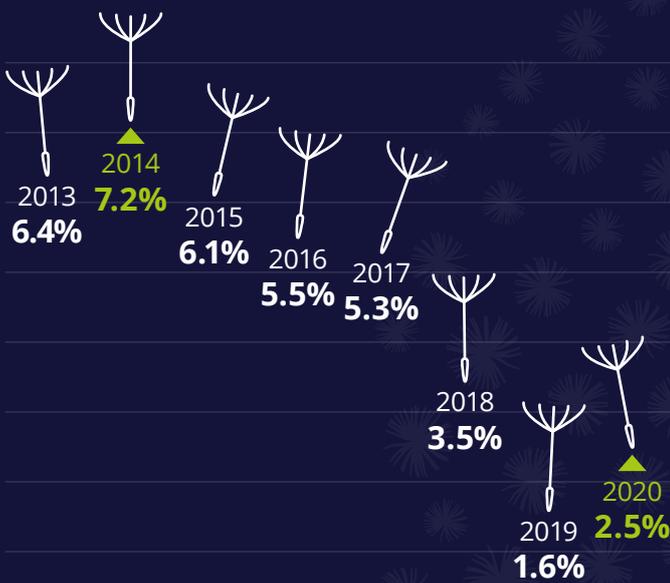
2019
1.6%

2020
2.5%

Despite regulatory steps to speed up development and approvals, the average cycle times for late-stage assets have continued to lengthen to a **seven-year high of 7.14 years**

2014: **6.15 years**

2019: **6.64 years**

2020: **7.14 years**

Cost to bring an asset to market **continues to increase** due to the growing complexity of development and longer cycle times

2013
$1.327bn

2019
$2.391bn
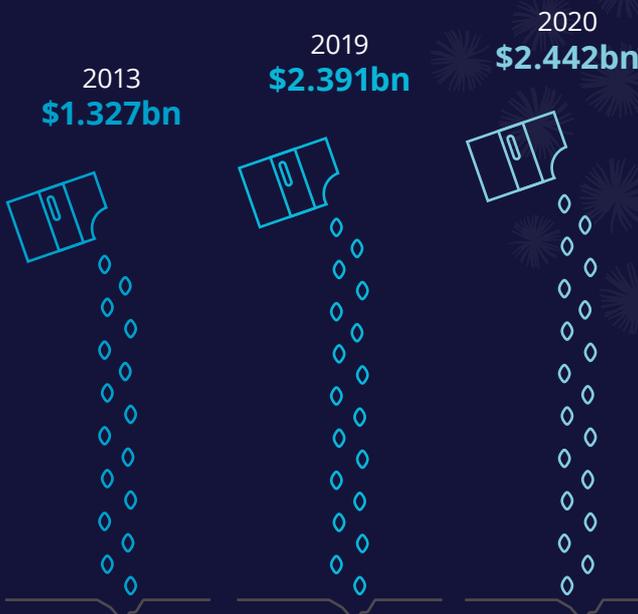
2020
$2.442bn

Potentially reversing the **overall decline** seen since 2013, average forecast peak sales **increased by 17.9%** from 2019 to 2020

2013
$520m

2019
$357m
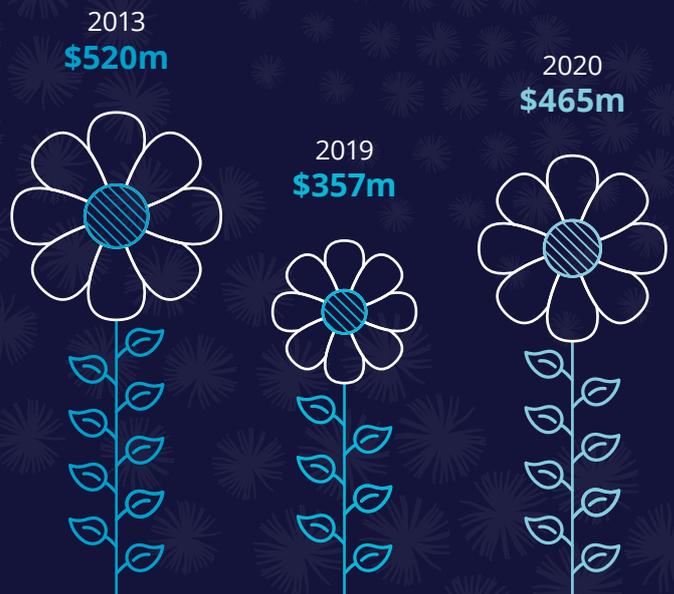
2020
$465m

COVID-19 impact

The pandemic has **negatively impacted cycle times** for an estimated **1,210 non-COVID trials** (between March and November 2020)

Of these, **29% were in Phase III**, which could affect future asset launches and sales

Oncology was the **most affected** therapy area, accounting for **nearly 26%** of all delayed or suspended trials

Future outlook for R&D

Greater regulatory flexibility

Greater focus on personalised and next gen therapies

Virtual/decentralised trials will become commonplace

Increasing use of digital technologies, AI and access to RWD/E

Preparing for this future requires

Adopting and scaling the use of transformative approaches

Investing in AI and digital technologies

Continuing the momentum of collaboration

Acquiring and retaining data science talent

Executive summary

Breakthrough advances in science and technology continue to fuel innovation in the biopharmaceutical (biopharma) industry and shape health care. However, though biopharma R&D is under mounting pressure, this year's analysis is showing a potential for growth with our cohort seeing small improvements in returns on pharmaceutical innovation. Nevertheless, peak sales remain at much lower levels than in 2013, despite a small uptick this year, and R&D costs continue to increase. Costs are increasing due to the growing complexity of development and longer cycle times. There is a pressing need to optimise processes and fundamentally change the drug development paradigm through use of digital and transformative approaches. COVID-19 has spurred on these changes and the industry is well-positioned to build on the momentum and look optimistically for a future with higher returns on pharmaceutical innovation.

Since 2010, our series of reports on *Measuring the return from pharmaceutical innovation* have provided insights into the state of biopharma R&D, by projecting the internal rate of return (IRR) on investment that 12 large-cap biopharma companies might expect to achieve from their late-stage pipelines. In 2015, we added an extension cohort of four more specialised companies and backtracked their R&D investments to 2013. Over time, our analysis has shown that both cohorts have seen large declines in their expected returns, and there has been convergence in the performance of the original and extension cohorts. Moreover, for the first time since our research began, a company in the original cohort acquired an extension cohort company. For these reasons, and for the purpose of this and future reports, we have combined the original and extension cohorts to create a 'combined cohort' of 15 companies. However, since this is a transition report, we also provide a comparative analysis of the performance of the separate cohorts. It should be noted that our analysis period was from May 2019 to April 2020 and, therefore, this report's pipeline of late-stage assets does not fully reflect the COVID-19 vaccines and therapies that have since emerged.

Measuring the return from pharmaceutical innovation

For the first time since 2014, the average IRR has had an uptick from the previous year, showing signs of a potential reversal in the declining trend. In 2020, the projected internal rate of return (IRR) for the combined cohort was 2.5 per cent, 0.9 percentage points higher than in 2019 but 3.9 percentage points lower than in 2013. The range between top and bottom performers narrowed from 2019 and was the third-lowest since 2013. While ten of the 15 biopharma companies in the combined cohort improved their average IRR from 2019, all but one are below the industry cost of capital. The projected IRR for the original cohort in 2020 was 1.7 per cent – an increase of 1 percentage point from 2019, but a decrease of 3.1 percentage points since 2013. The three-company extension cohort, in contrast, had a projected IRR of 6.6 per cent in 2020, up from 5.2 per cent in 2019 but well below the 17.4 per cent achieved in 2013.

In measuring IRR (as a proxy of R&D productivity) we factor in the average cost to develop the assets in each company's pipeline and the expected sales from these assets once launched (see Methodology).

- For the seventh year since 2013 the average cost to develop an asset, including the cost of failure, increased for the combined cohort. In 2020, the average cost to develop an asset was $2,442 million, a small increase of $51 million compared to 2019 and a $1,115 million increase since 2013.

- The increase in costs was due mainly to a fall in the overall number of assets in late-stage pipelines. In 2020, the companies in the combined cohort had a total number of 207 late-stage assets, a decrease from 213 in 2019, with an average of 13.8 per company but a wide variation across companies (between six and 23).

- In 2020, our combined cohort has seen an increase in average forecast peak sales per pipeline asset for the combined cohort to $421 million from $357 million in 2019. The variation in the range of forecast peak sales across companies has narrowed and is the smallest yet.

We have also seen a change in the sources of innovation. Until recent years, over half of the late-stage pipelines of both cohorts were sourced through internal innovation. However, in the past three years the original cohort companies have relied on external sources for more than 50 per cent of their late-stage pipeline. The same trend is evident in the extension cohort over the past two years. This trend of more innovation coming from external sources is indicative of big pharma companies seeking to augment their innovation pipeline through acquisitions, collaborations and scientific partnerships with other (often smaller) players. This also supports our observation that the extension cohort companies over time have become more like the original cohort, and are more likely to partner to access capability and innovation.

Longer cycle times remain a challenge to biopharma R&D

This year's analysis shows that the trend towards longer cycle times has continued. The average clinical cycle time (from the start of Phase I to completion of Phase III) for the combined cohort reached a seven-year high of 7.14 years in 2020. This has been driven by the growing complexity of drug development; increasing competition in enrolling participants for clinical trials and difficulties in retaining them; as well as complex data capture, collection, and management to satisfy regulatory requirements. Since the start of our report series, there has also been an increasing shift in the pipeline of most companies towards oncology, whose cycle times are twice as long as those for other therapy areas. This is mainly because oncology trials involve complex protocols with stringent selection criteria, making it difficult to identify and recruit eligible patients.

In addition, companies across the industry have been developing more targeted and complex therapies, including biologics and new modalities to address unmet needs in smaller patient population or subgroups. Advances in scientific innovation have led to a greater focus on developing new modalities such as next generation therapies, adding to the complexity of drug development and consequently increasing the timelines.

Regulators have introduced several new regulatory pathways (through the creation of special designations) to expedite the development and approval of new drugs and accelerate patient access to life-saving and innovative therapies. However, this has done little to reduce development times. Our analysis shows that although a growing number of late-stage assets of the combined cohort have received a special designation (90 out of 207 assets in 2020 up from 87 out of 213 in 2019), the average clinical cycle time has continued to lengthen. Accelerated pathways alone are not sufficient to shorten the time for clinical development. There is an immediate need to optimise processes or fundamentally change the drug development paradigm, as the 'need for speed' is perhaps the most vital factor for improving R&D productivity.

The recent decline in IRR and rising cycle times come at a time when emerging technologies and transformative approaches to drug development are enjoying experimental success. Over the past few years, biopharma companies have begun tapping the potential of digital transformation through the application of artificial intelligence (AI) and digital technologies for these purposes, and the COVID-19 pandemic has accelerated the rate of adoption. Our research has found that most biopharma companies are attempting to integrate AI into drug discovery and development processes to transform many of the key steps in clinical trials, from protocol design to study execution. The use of transformative approaches to drug development such as master protocols, adaptive trial design, enhanced segmentation of patients and disease, and use of real-world evidence (RWE) are beginning to gain momentum; but upscaling their use will be essential to reduce cycle times.

The COVID-19 experience: Sowing the seeds of change for the future of biopharma R&D

The COVID-19 pandemic has had a devastating impact on people's lives. While it has also disrupted clinical trials across the globe, the pandemic has required the industry to adopt new approaches to R&D. Although new approaches were being piloted, the pandemic has accelerated the adoption of digital technologies at scale and in a much shorter time-frame than many believed would be possible. The pandemic not only accelerated the adoption of digital technologies in clinical trials, but also led to the development of a number of novel COVID-19 vaccines and therapies in record time through extraordinary collaboration and partnerships. These positives arising from the COVID-19 experience have sown the seeds of change for a more productive future for biopharma R&D. Moreover, the accelerated development of COVID-19 therapies and vaccines is expected to have a positive impact on the industry IRR over the coming years.

What's next for biopharma R&D and how should companies prepare?

We predict that post-pandemic the seeds of change will continue to accelerate the transformation of the industry towards a new future for R&D, in which new technologies and wide use of innovative approaches could reverse the decline in IRR. However, these seeds of change sown during the pandemic must be nurtured. This will require companies to take steps to continue collaborating, expand the use of digital technologies to run decentralised and virtual clinical trials, and adopt at scale transformative approaches to expedite drug development. It will require companies to attract and retain people with relevant skills and talent, including data scientists and bioinformaticians, and also skilled interdisciplinary leaders who are AI-friendly and tech-savvy and willing to embrace new business and operating models.

Measuring the return from pharmaceutical innovation

Our annual *Measuring the return from pharmaceutical innovation* report series continues to demonstrate the need for transformational change in the R&D business and operating model of companies to reverse the downward trend in R&D returns across the biopharma industry. Our 2020 analysis shows a potential reversal of the declining trend in projected IRR, with an uptick in the average return for the companies in our cohorts.

2020 has seen an uptick in projected returns from innovation – beginning to reverse a decade of decline?

Over the past few years, we have seen a convergence in the performance of our original and extension cohorts. Moreover, with the Celgene portfolio moving into Bristol-Myers Squibb, our extension cohort now comprises three companies whose investments in R&D place them in the top 15 biopharma investors. Therefore, in this year's analysis, and for future years, we are combining the two cohorts, to form a 'combined cohort' (see sidebar: A transition year).

Figure 1 shows the overall trend line for IRR between 2013 and 2020 for the combined cohort. It should be noted that, as we are continually working to improve the methodology and modelling underpinning this analysis, numbers from 2019 have been re-stated following our data provider's development of an AI-enabled predictive model for probability of phase transition (see Methodology for more details). For the first time since 2014, the average IRR has had an uptick from the previous year, showing signs of a potential reversal in the declining trend. The combined cohort has seen a consolidated average IRR of 2.5 per cent in 2020, an increase from 1.6 per cent in 2019 but an overall decrease from 6.4 per cent in 2013.

The range between top and bottom performers in the combined cohort has narrowed from 30 percentage points in 2013 (top performer: 26.5 per cent, bottom performer: -3.5 per cent) to 22 percentage points in 2019 (top performer: 10.3 per cent, bottom performer: -11.7 per cent) and now 18.9 percentage points in 2020 (top performer: 14.5 per cent, bottom performer: -4.4 per cent). In addition, while ten of the 15 biopharma companies in the combined cohort improved their average IRR in 2020 compared to 2019, all but one are below the industry cost of capital. On a three-year rolling average basis, the average IRR of the combined cohort is at 2.5 per cent for 2018-20 (Figure 20 in Appendix).

Figure 1. Return on late-stage pipeline, 2013-20 – combined cohort
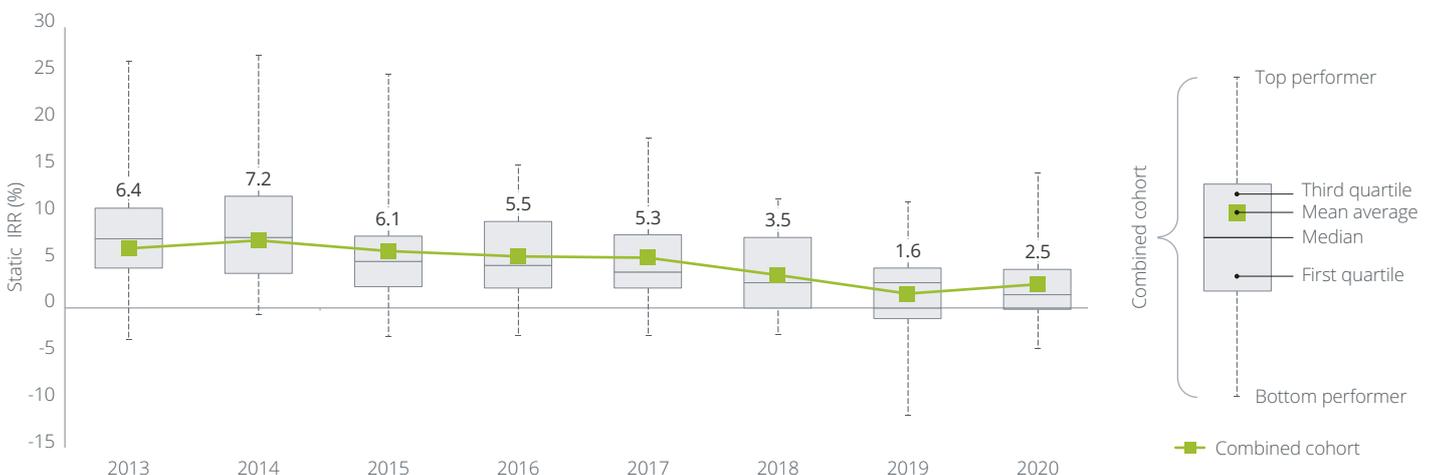
Note: 2019 numbers have been restated. For more information, see Methodology.
Source: Deloitte LLP, 2021.

Figure 2. Return on late-stage pipeline, 2010-20 – original and extension cohorts
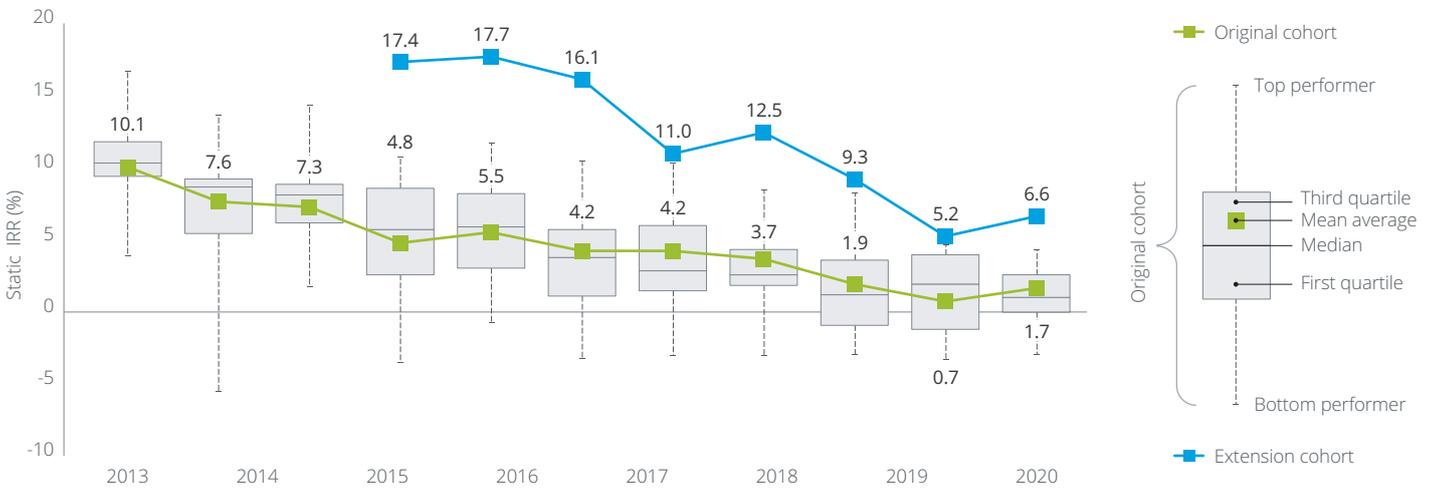
Note: 2019 numbers have been restated. For more information, see Methodology.

Source: Deloitte LLP, 2021.

A transition year

This is a transition year for our *Measuring the return from pharmaceutical innovation* series. In the past year, one of the companies in our original cohort acquired one of the extension cohort companies. Furthermore, the extension cohort companies can no longer be differentiated in terms of scale or even pharmaceutical R&D spending from the companies in the original cohort. This report will therefore present a combined analysis throughout for all 15 companies but will also show some results separately for the original and extension cohorts, for comparison with previous years.

Importantly, in the future we will expand our analysis to measure the IRR of the top 20 R&D pharma spenders to get a more accurate picture for the overall industry. We will start reporting on this top 20 cohort in our next report as we begin to see year-on-year performance trends.

Moreover, as we are continually working to improve the methodology and modelling underpinning this analysis, numbers from 2019 have been re-stated following our data provider's development of an AI-enabled predictive model for probability of phase transition. In addition, re-adjusting and re-stating 2019 numbers allows for a more accurate comparison with 2020. As the overall declining trend seen since 2010 remains the same, numbers referring to years prior to 2019 remain as stated in our 2019 report which were obtained with the best available information at the time of performing the analysis.

Figure 2 shows the average IRR for the original and extension cohorts. For the companies in the original cohort, the average IRR increased in 2020 to 1.7 per cent – 1 percentage point higher than in 2019, and a fall of 8.4 percentage points from 2010. In comparison, the now three-company extension cohort had an average projected IRR of 6.6 per cent in 2020, up from 5.2 per cent in 2019.

Figure 3 presents the aggregate drivers of change for the combined cohort between 2013 and 2020, and between 2019 and 2020. For comparison, drivers of change in IRR over the past decade (2010-20) for the original cohort and from 2013 to 2020 for the extension cohort are shown in Figure 21 in the Appendix. Year-on-year drivers of change in IRR for the combined cohort from 2013 to 2020 are shown in Figure 22 in the Appendix.

Figure 3. Drivers of change in IRR - combined cohort

2013-20

2019-20

Note: 2019 numbers have been restated. For more information, see Methodology.

Source: Deloitte LLP, 2021.

Between 1 May 2019 and 30 April 2020, the combined cohort had a total of 53 approved assets, an increase from 39 in 2019, with forecast total sales of $188 billion, representing a 3.0 percentage point decline in projected returns. In 2020, terminations resulted in a 0.2 percentage point decline in IRR (smaller than the decline between 2018 and 2019). Since 2013, the overall effect of terminations has been a fall in IRR of 4.0 percentage points for the combined cohort of companies.

As we have seen every year in our *Measuring the return from pharmaceutical innovation* series, companies continue to innovate by investing in new assets. However, the rate at which companies have been replenishing their late-stage pipeline value has historically not been sufficient to compensate for the successful approval and flow of value into the commercial pipeline and loss through late-stage attrition.

In 2020, there was an increase in IRR of 2.2 percentage points due to 45 new assets entering the pipeline of the combined cohort, down from the 59 new assets that entered the pipeline in 2019. These new assets have forecast lifetime sales of $334 billion. The value of projected returns from existing late-stage pipeline assets of our combined cohort companies was the second-highest positive driver in IRR, with an increase of 1.8 percentage points, between 2019 and 2020. This increase in forecast revenues from existing assets was driven largely by positive trial data for high-value assets.

The average number of assets in development has stayed relatively flat

In 2020, the companies in the combined cohort had a total number of 207 late-stage assets, a decrease from 213 in 2019, with an average of 13.8 per company but a substantial variation across companies (from six to 23) (Figure 4). The reason for the increase in the average number of assets, despite the decrease in their total number, is due to the merger of two companies in our combined cohort, which reduced the denominator from 16 to 15.

The average cost to develop an asset in the combined cohort has slightly increased

In 2020, the companies in our combined cohort spent $96.8 billion on R&D, which is an increase of 34 per cent in underlying annual R&D expenditure since 2010. In 2020, their average cost to develop an asset was $2,442 million, an increase of $51 million from 2019 and $1,115 million from 2013 (Figure 5). This average cost increase was due mainly to the overall reduction in the number of assets in the late-stage pipeline.

The wide variation between companies in average costs per asset in Figure 5 is a result of combining the two different cohorts. On a three-year rolling average basis, the average R&D cost per asset for 2018-20 was $2,366 million (Figure 23 in Appendix).

Figure 6 shows the trend line in average costs for the original and extension cohorts from 2010 to 2020. For the first time since 2015 the average cost to develop an asset for companies in the original cohort was higher than for those in the extension cohort.

Figure 4. Average number of assets in late-stage pipeline, 2013-20 – combined cohort
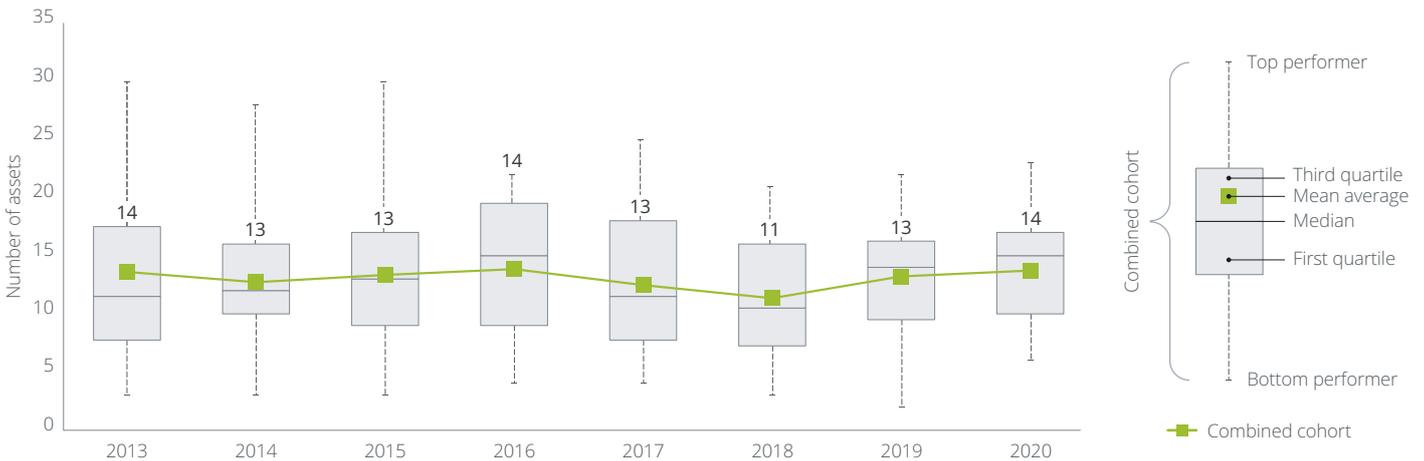
Source: Deloitte LLP, 2021.

Figure 5. Average R&D cost to develop a compound from discovery to launch, 2013-20 – combined cohort
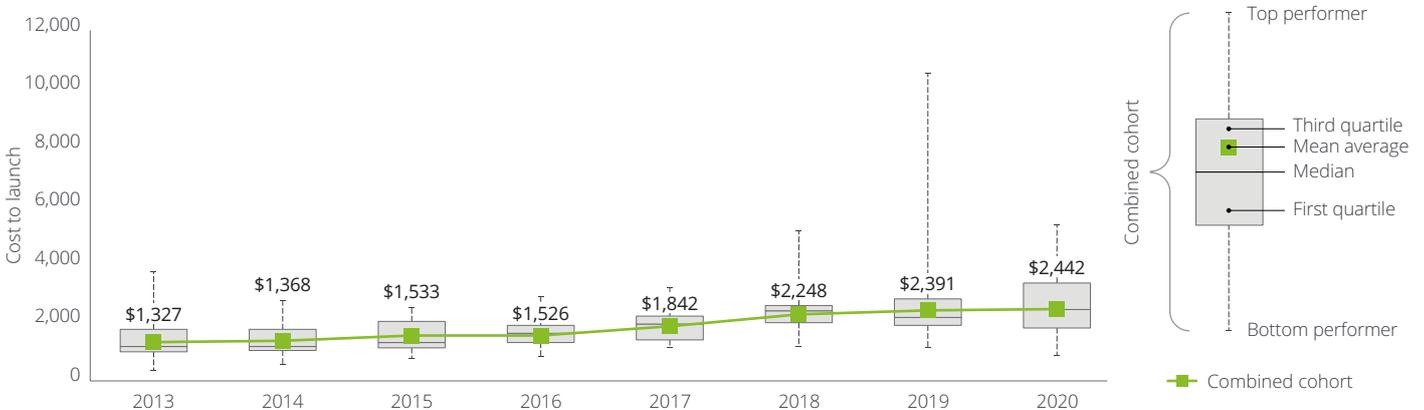
Note: 2019 numbers have been restated. For more information, see Methodology.
Source: Deloitte LLP, 2021.

Figure 6. Average R&D cost to develop a compound from discovery to launch, 2010-20 – original and extension cohorts
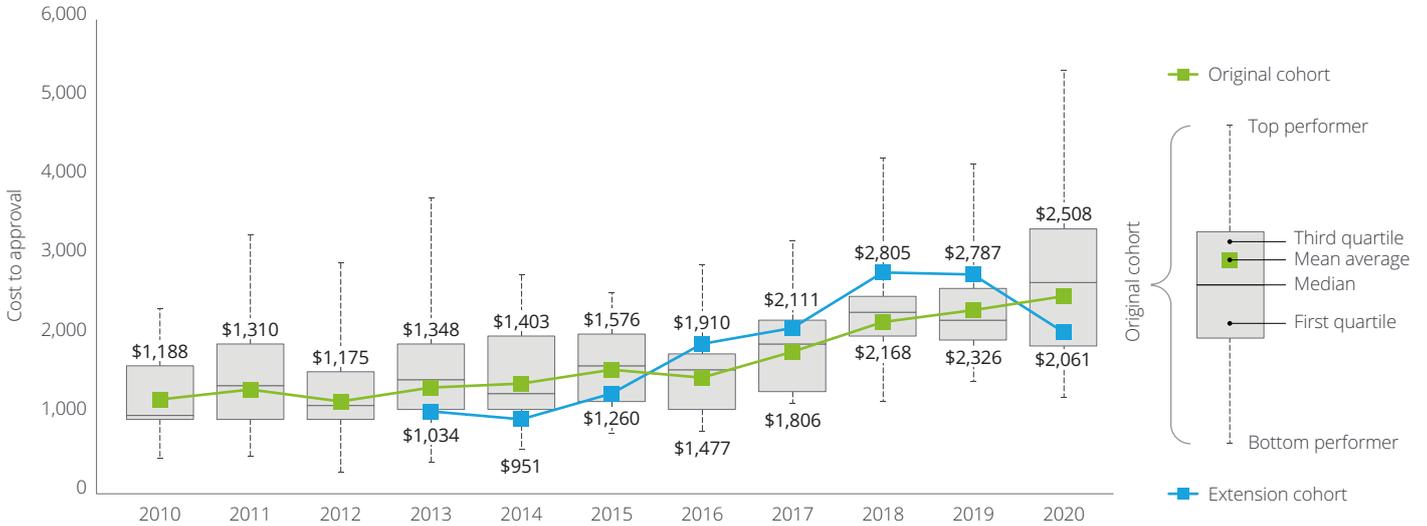
Note: 2019 numbers have been restated. For more information, see Methodology.

Source: Deloitte LLP, 2021.

Figure 7. Average forecast peak sales per pipeline asset, 2013-20 – combined cohort
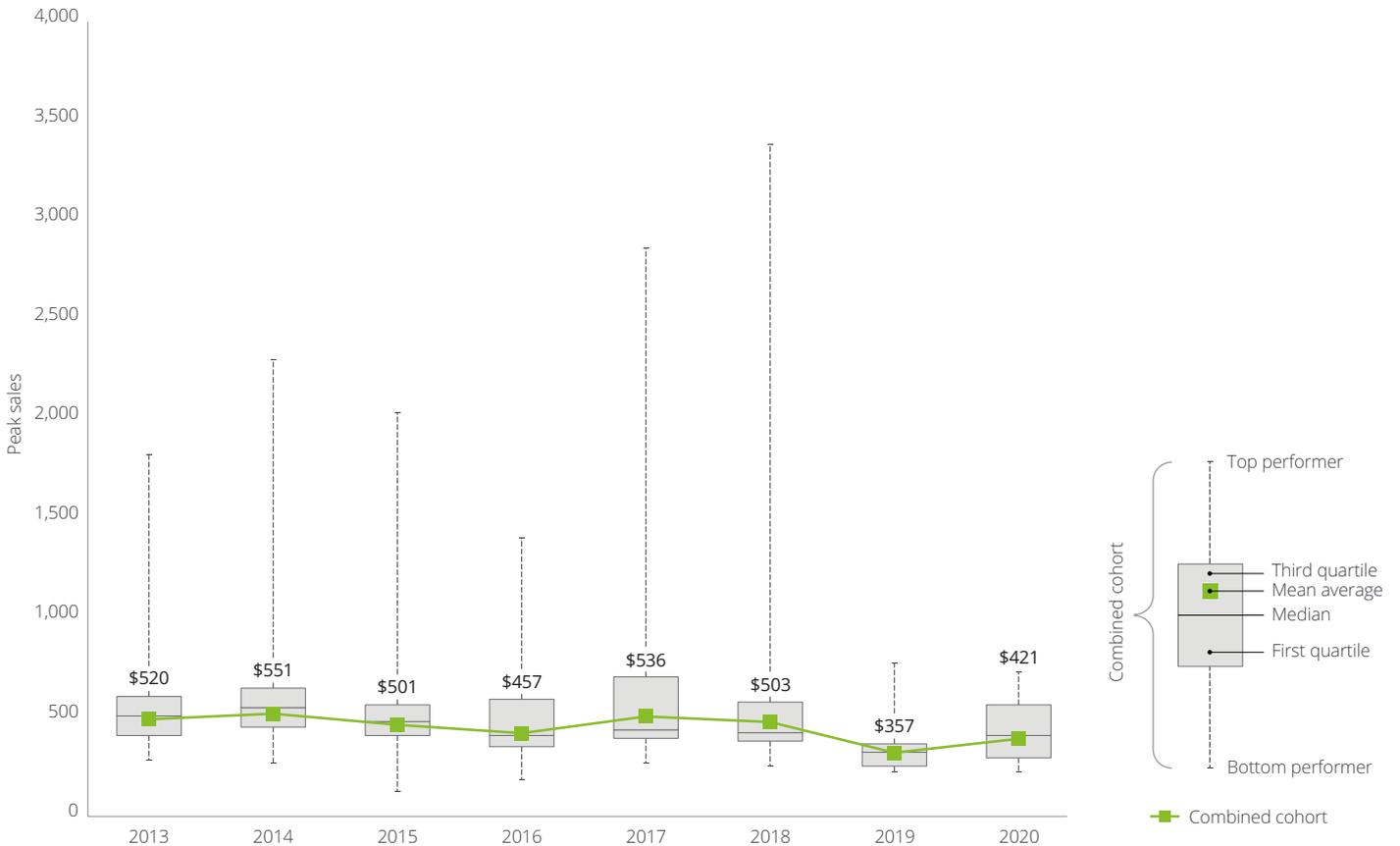
Note: 2019 numbers have been restated. For more information, see Methodology.

Source: Deloitte LLP, 2021.

Figure 8. Average forecast peak sales per pipeline asset, 2010-20 – original and extension cohorts
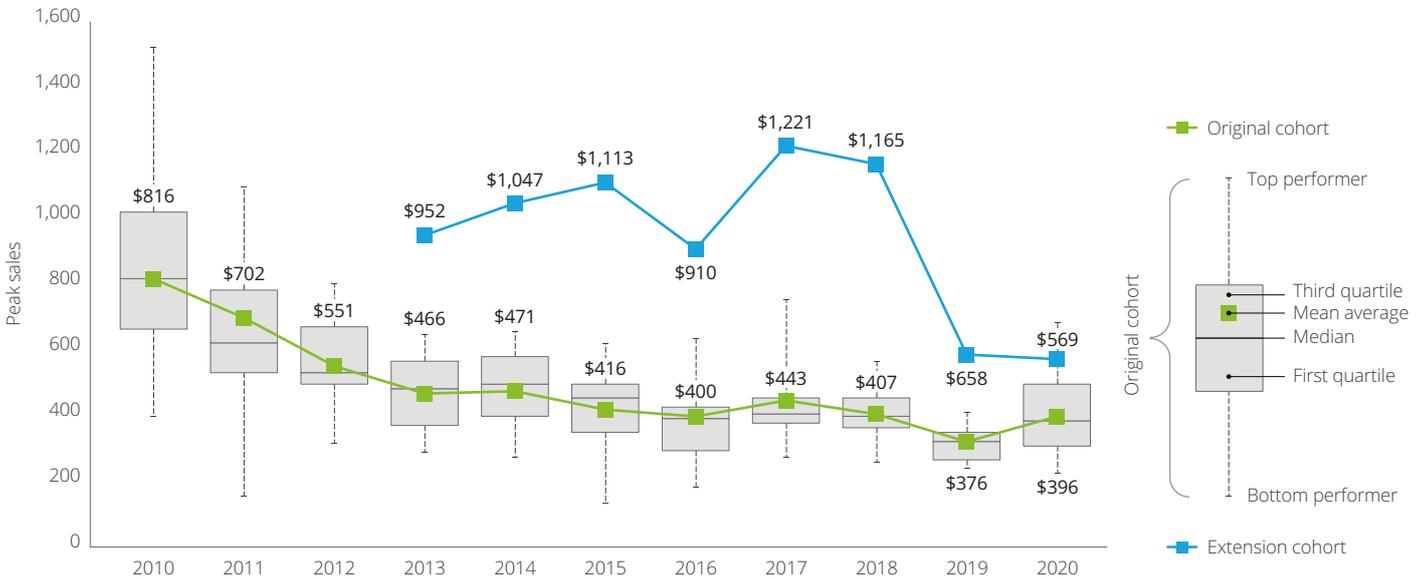
Source: Deloitte LLP, 2021.

Average peak sales increase in 2020

In 2020 there was a 17.9 per cent increase in average forecast peak sales per pipeline asset for the combined cohort from 2019, with $421 million in 2020 from $357 million in 2019. Variations between companies in the range of forecast peak sales were the smallest since 2013 (Figure 7). On a three-year rolling average basis, the average forecast peak sales per asset for 2018-20 was $423 million (Figure 24 in Appendix).

Figure 8 shows the trend line in average forecast peak sales per pipeline asset for the original and extension cohorts from 2010 to 2020. The average forecast peak sales for the extension cohort decreased yet again, whereas the original cohort has seen a slight increase.

Sources of innovation for biopharma are increasingly external

For the first seven years of our analysis, the sources of innovation for the late-stage pipelines of both the original and extension cohort companies were predominantly through internal innovation. However, in the past three years the original cohort companies have relied on external sources for more than 50 per cent of their late-stage pipeline. We have seen the same trend in the extension cohort in the past two years (Figure 9). Notably, the original cohort has seen a similar increase in the contribution to the late-stage pipeline from M&A and co-development over the past three years (compared to previous years).

This trend of sourcing more innovation from external sources is indicative of big pharma companies seeking to augment their innovation pipeline through acquisitions, collaborations and scientific partnerships with other (often smaller) players. Strikingly, the extension cohort has also increased markedly its reliance on co-development (from 26 per cent in 2019 to 61 per cent in 2020, especially when compared to 2017 when 60 per cent was self-originated). This supports our proposition that the extension cohort companies have become more likely over time to partner in order to access capability and innovation, and in so doing have become more like the original cohort.

Figure 9. Proportion of late-stage pipeline sourced from internal and external sources, 2010-20 – original (top) and extension (bottom) cohorts
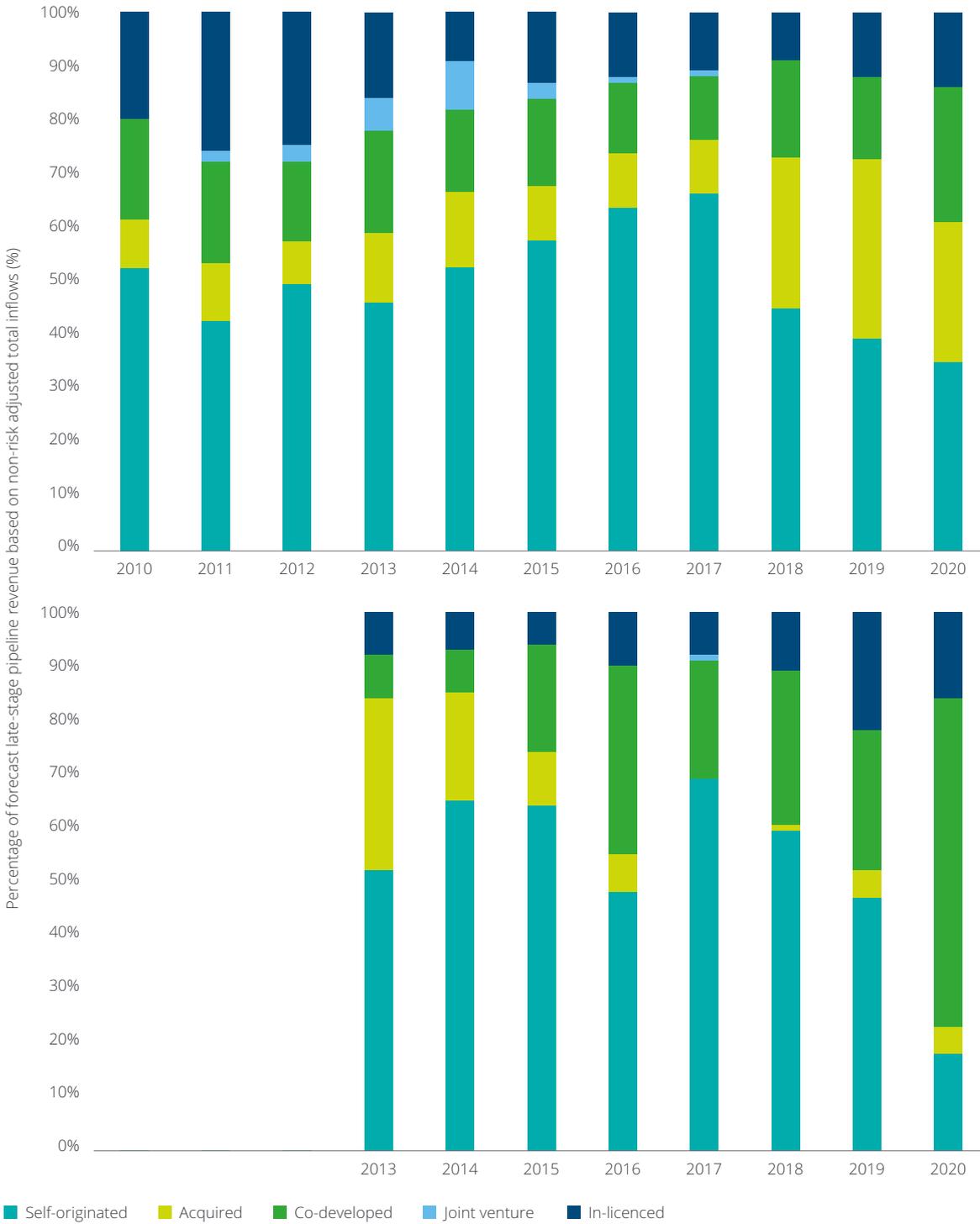
Source: Deloitte LLP, 2021.

Longer cycle times remain a challenge for biopharma R&D

This year's analysis suggests the trend towards longer cycle times has continued. Despite the small uptick in 2020, we have seen an overall decline in IRR, which highlights a need to optimise existing processes and fundamentally change the development paradigm. This 'need for speed' is perhaps the most vital factor for improving productivity, recognising that many of the underlying costs are hard to control. From protocol design to study execution, companies are attempting to integrate AI and other digital technologies into their existing development processes. While the use of transformative approaches to drug development such as master protocols, adaptive trial design, enhanced segmentation of patients and diseases, and use of real-world evidence (RWE) are beginning to gain momentum; upscaling their use will be essential if companies are to reduce cycle times.

Cycle times continue to have a negative impact on R&D productivity

Clinical trial cycle times have continued to lengthen. For the combined cohort, the average clinical cycle time (from the start of Phase I to completion of Phase III) reached a seven-year high of 7.14 years in 2020 (Figure 10). This has been driven by the growing complexity of drug development; increasing competition in enrolling and difficulty retaining participants in clinical trials; and inefficient data capture, collection, and management. Reducing cycle times remains a pressing concern for an industry struggling to improve its R&D productivity.

Figure 10. Average cycle times (in years), 2014-2020 – combined cohort
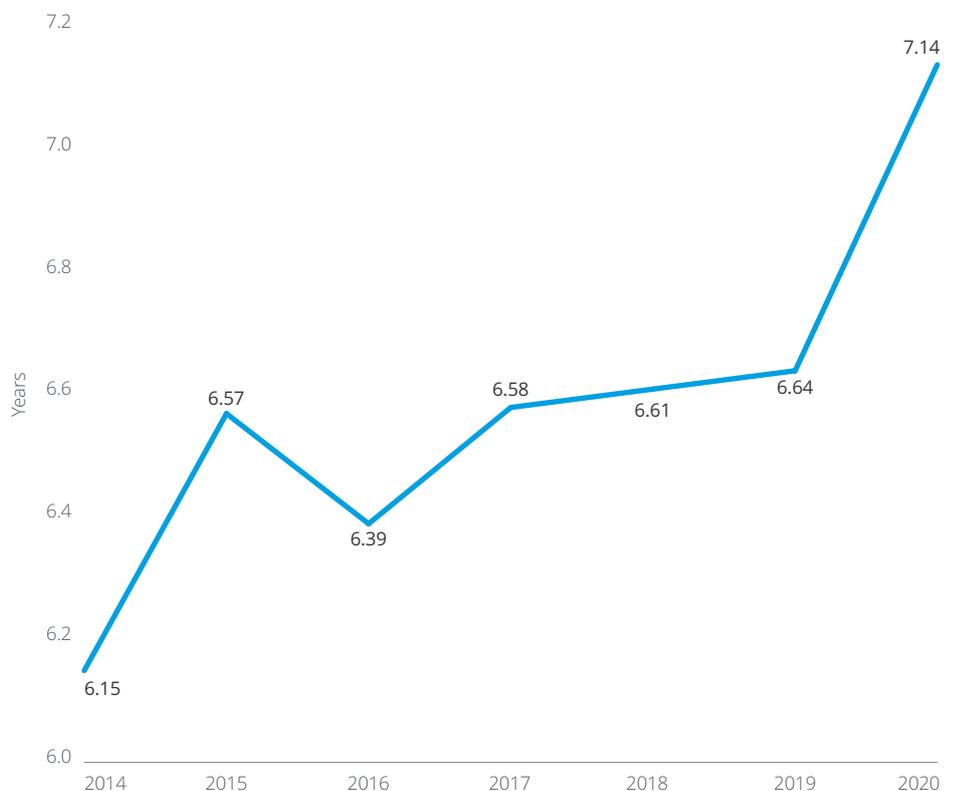
Note: Figures indicate time from start of Phase I trial to completion of Phase III trial.
Source: Deloitte LLP, 2021.

In the past few years, our analysis has shown a shift in the pipeline for the combined cohort towards oncology (Figure 11). Moreover, oncology trial cycle times have continued to lengthen and are twice as long as the cycle times for infectious disease and the central nervous system (CNS) (Figure 12). This is mainly because oncology trials involve complex protocols with stringent participant selection criteria that result in longer recruitment times for patients. Trial protocols have also expanded to capture diverse data and new endpoints (such as genomics, imaging data, and patient-reported outcomes) to satisfy the access and reimbursement requirements of multiple stakeholders.

At the same time, a deeper understanding of the genetic and molecular basis of disease and biomarkers has enabled precision segmentation of disease and patient sub-populations. Companies both within and outside our cohorts have been developing targeted and complex therapies, including biologics and new modalities to address unmet needs in smaller patient populations or subgroups (see sidebar: New modalities are forming an increasing share of the pipeline). Oncology is one such area, where more therapies are being developed for rare and distinct cancer sub-types.

Figure 11. Late-stage pipeline proportion of assets by therapy area, 2013-2020 – combined cohort
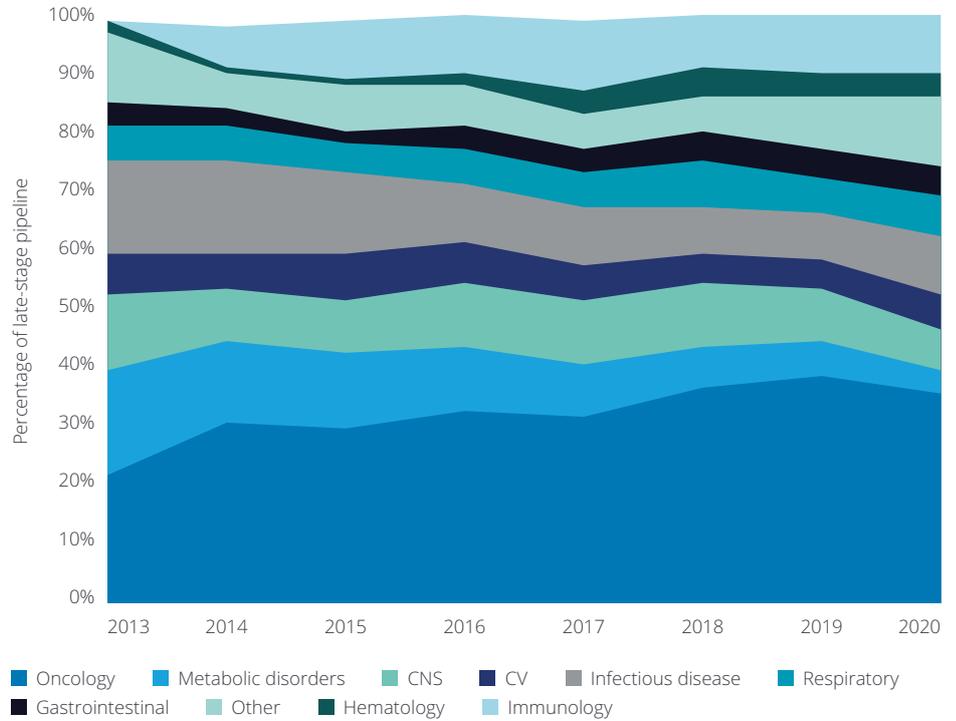
Note: CNS = central nervous system and CV = cardiovascular.
Source: Deloitte LLP, 2021.

**Figure 12. Clinical trial cycle time by therapy area, 2016-2020 – combined cohort**
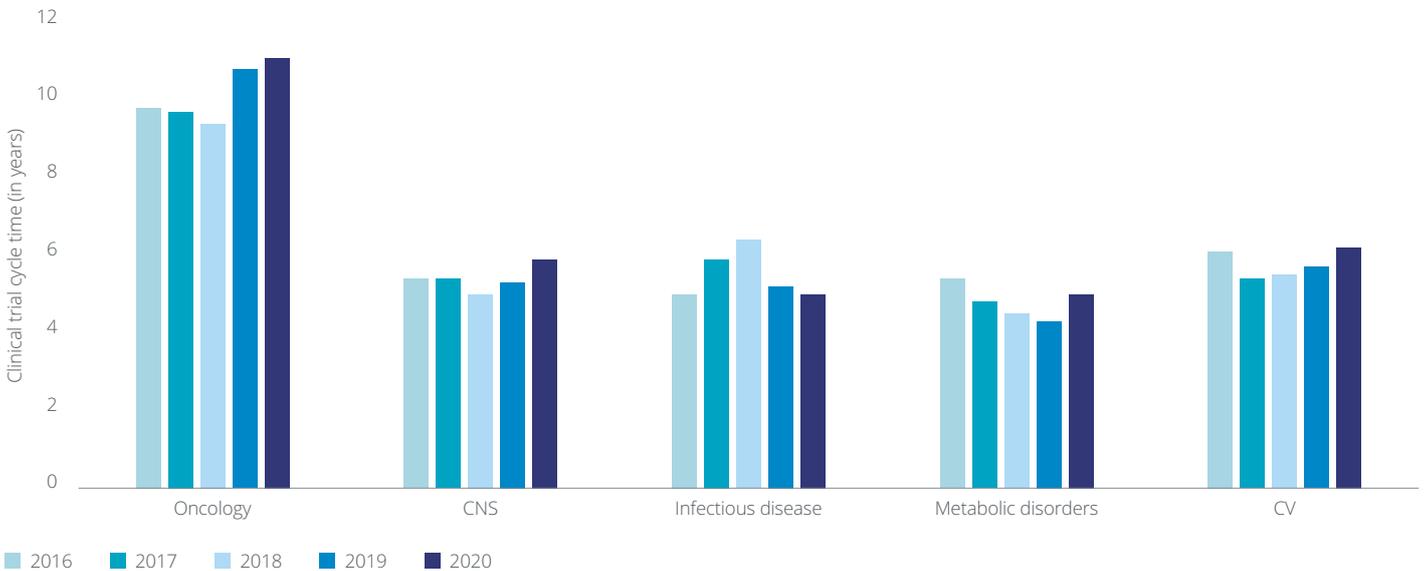
Note: Figures indicate time between start of Phase I trial to completion of Phase III trial.
Source: Deloitte LLP, 2021.

New modalities are forming an increasing share of the pipeline

While small molecules and biologics continue to remain a crucial component of the pipeline, advances in scientific innovation have prompted a focus on developing new modalities such as cell and gene therapies, adding to the complexity of drug development. These new types of therapy are enabled by a diverse set of technological platforms, including CAR-T, stem cells, oligonucleotides and gene editing.

Biopharma is now on the cusp of a new wave of innovation, as next generation therapies are forming an increasing share of the pipeline. For the companies in the combined cohort, next generation therapies (cell and gene therapies, oligonucleotide therapies and protein-based therapies) accounted for 18 per cent of assets in the pipeline in 2020, compared to just nine per cent in 2013 (Figure 13).

For the top 20 biopharma companies by R&D spend, next gen therapies accounted for 13.4 per cent of late-stage pipeline assets in 2020. Our analysis suggests that revenue from next gen therapies for these companies is expected to grow to $14.6 billion in 2030 from an estimated $1.4 billion in 2021. As new proof points emerge about the safety and efficacy of these therapies, and as coverage models evolve, companies will have to consider how to capitalise on the opportunities presented by new modalities, which may require increased investment but could potentially provide higher returns.

Figure 13. Pipeline focus by modality, 2013-2020 – combined cohort
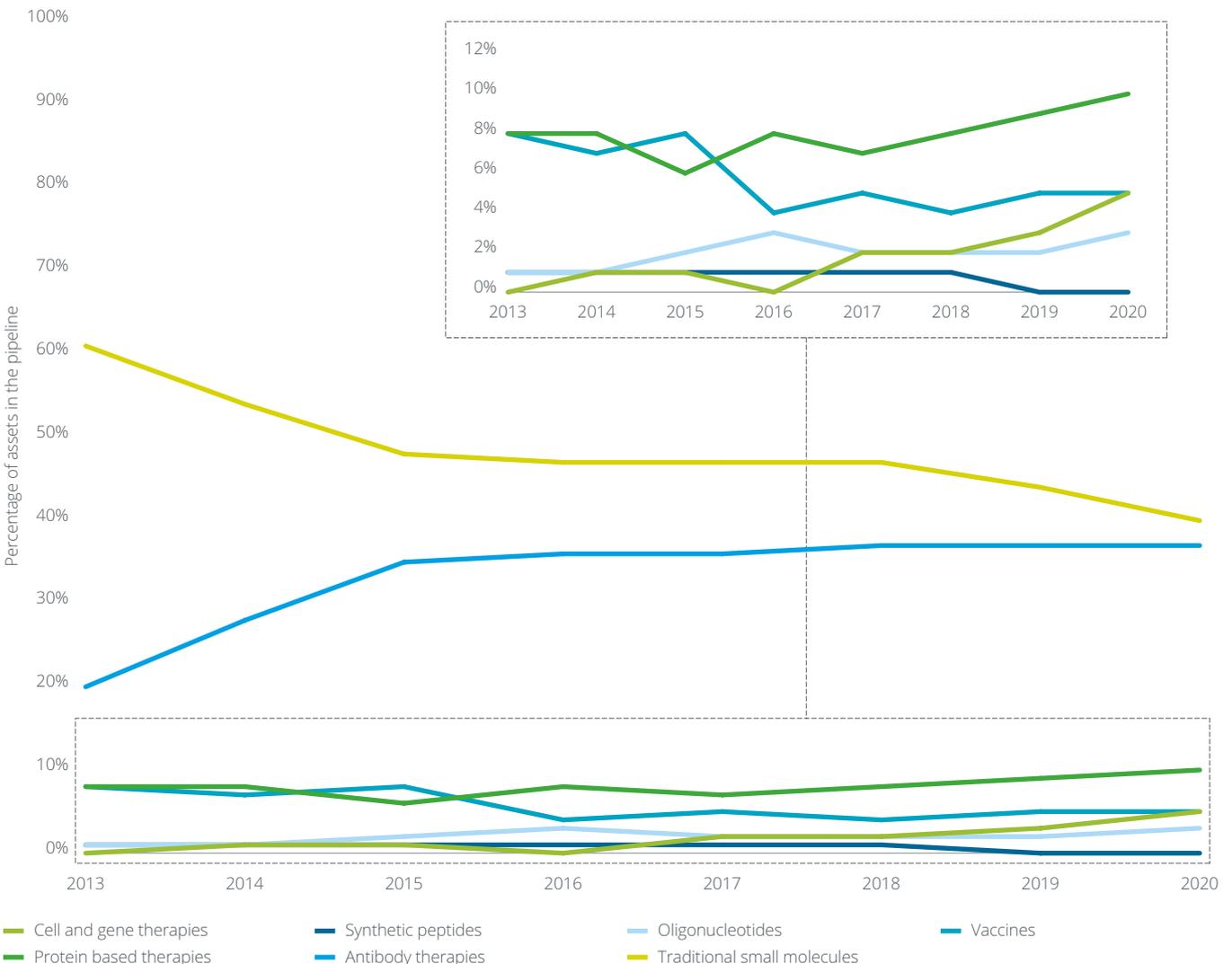
Source: Deloitte LLP, 2021.

Figure 14. Clinical cycle time versus number of pipeline assets with special designations, 2014-2020 – combined cohort
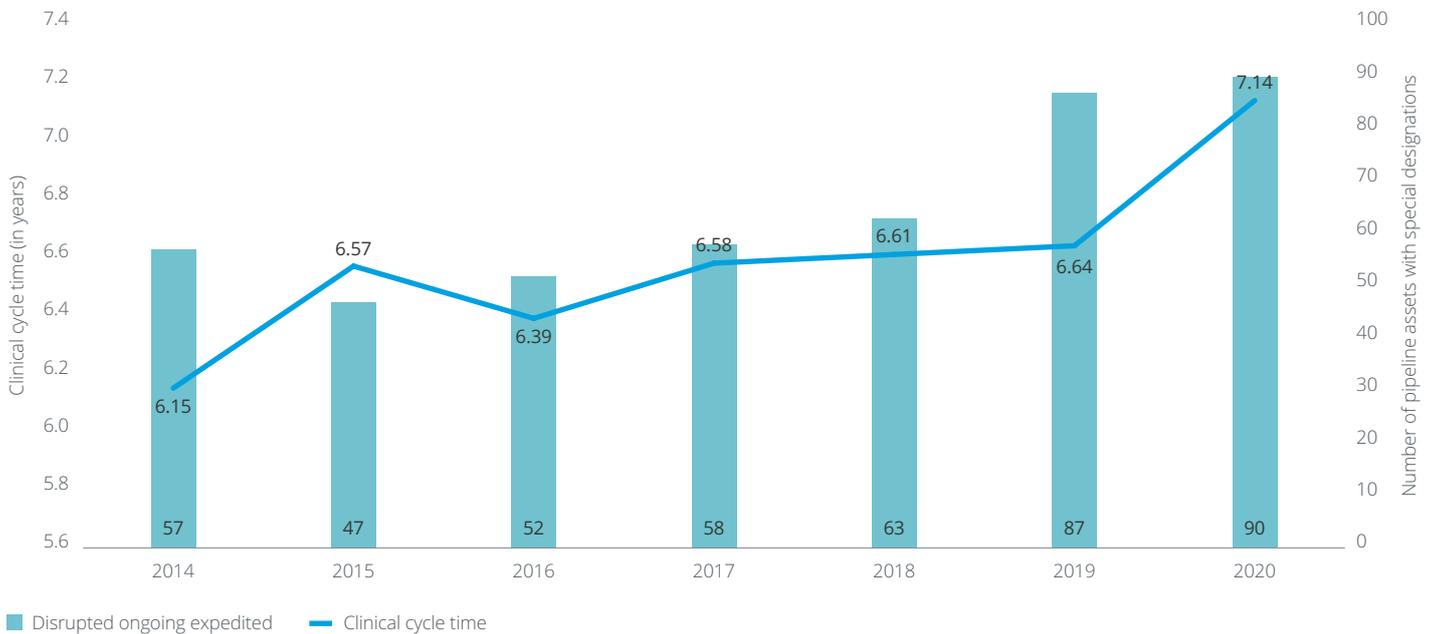
Note: Special designations include assets with breakthrough, fast track, accelerated approval, priority review and orphan drug status.
Source: Deloitte LLP, 2021.

The growing complexities of drug development and increasing numbers of oncology trials have made it difficult to enrol and retain trial participants. Only a small number of eligible patients participate in clinical studies. Even though oncology trials may offer access to life-saving therapies, studies show that only two to nine per cent of adult patients participate in trials.[1] The growing number of therapies targeted at unmet needs and smaller patient subgroups has increased the competition to recruit from the limited pool of available trial participants. The need to visit sites frequently has reduced the willingness of individuals to participate and has resulted in high drop-out rates. Recent data suggest that 18 per cent of participants drop out after enrolling, with difficulty attending clinical visits cited as a major reason.[2] These factors have created delays in trial execution to a point where 86 per cent of all trials do not meet enrolment timelines and 80 per cent are delayed due to recruitment issues.[3]

Today, clinical trial data management continues to involve staff and investigators recording data into multiple disconnected sponsor and CRO systems.[4] In fact, six or more systems are typically used in a trial. In addition, several documents (such as case report forms and study protocols) have to be created during the clinical trial, requiring manual data transcription from multiple documents and systems. This can result in errors and inconsistencies, and consequently the need for reworking data, which will ultimately delay trial progress and dossier submission.

Amid growing cycle times, regulators have put in place several pathways (through the creation of special designations) to expedite the development and approval of new drugs and accelerate patient access to life-saving innovative therapies. However, despite a growing number of late-stage assets of the combined cohort receiving a special designation, average clinical cycle times have continued to lengthen (Figure 14).

This points to the immediate need to optimise processes or fundamentally change the development paradigm through the use of innovative approaches.

The growing complexities of drug development and increasing numbers of oncology trials have made it difficult to enrol and retain trial participants.

AI and digital technologies are being applied increasingly to improve R&D productivity

The decline in IRR and longer cycle times point to the need to improve the efficiency of drug discovery and development. Over the past few years, biopharma companies have started to tap the potential of AI and digital technologies for these purposes and COVID-19 has further increased the focus on their use.

Our *Intelligent drug discovery: Powered by AI* report found biopharma companies are attempting to integrate AI into drug discovery processes, either through partnerships with start-ups and technology companies or by building internal AI capabilities. This includes using machine learning (ML) and deep learning (DL) to analyse the growing volume of clinical and research data to find new disease-associated targets, screen small molecule libraries to identify potential candidates, design new drug candidates, repurpose existing drugs to treat new diseases (see case study 1), and expedite pre-clinical testing. However, upscaling the use of AI in drug discovery will require access to robust and reliable data through consortia and partnerships, specialised AI expertise, and new metrics to evaluate the progress of AI drug discovery projects.

The industry has increasingly been experimenting with AI and digital technologies to transform many of the key steps in clinical trials, from protocol design to study execution. Our *Intelligent clinical trials* report highlights six case studies on the use of AI and digital technologies in drug development. Some of these uses, together with two new case studies, include:

- AI and advanced analytics can be applied to historical trial data to extract meaningful patterns of information for improving trial design and study planning. Some companies are already using AI tools to model the impact of site selection on enrolment and study timelines, to forecast resource requirements such as staffing and time commitments, and to predict clinical trial costs.[6]

- ML and DL can be used to analyse data from multiple sources to reduce the heterogeneity of study populations, and to select patients most likely to respond to treatments (predictive enrichment) and more likely to have measurable endpoints (prognostic enrichment), improving the probability of trial success.

- AI algorithms are already being used to mine publicly available web content (including digital trial announcements, trial databases and social media), to match patients with relevant trials (see case study 2).

- Together with wearables and mobile apps, AI can be used to monitor and engage patients, digitalise standard clinical assessments and automate data capture. AI-driven digital data flow solutions can integrate trial data from multiple sources to create standardised digital data elements. These data elements/inputs can be used to auto-populate required documents and reports, such as case reports and dossiers, quickly and without errors. Some companies are assessing the feasibility of using AI to manage clinical trial data (see case study 3).

The industry has increasingly been experimenting with AI and digital technologies to transform many of the key steps in clinical trials, from protocol design to study execution.

CASE STUDY 1

AI enables repurposing an arthritis treatment for use against COVID-19

The scale and urgency of the pandemic triggered the need to analyse already-approved drugs for use against the virus and quickly transition these to large scale trials. Using its AI platform, BenevolentAI, a drug discovery company, set out to identify approved drugs that could potentially stop the progression of COVID-19. In February 2020, BenevolentAI published findings in the Lancet, that Eli Lilly's baricitinib, a drug used to treat rheumatoid arthritis, could serve as a COVID-19 therapy and interrupt the passage of SARS-CoV-2 into cells. After the initiation of clinical trials in April, barcitinib was granted Emergency Use Authorisation by the US FDA in November 2020, based on results from clinical trials, to treat hospitalised COVID patients who require supplemental oxygen or invasive mechanical ventilation.[5]

Transformative development approaches to reduce cycle time are beginning to gain momentum

Transformative approaches to drug development have the ability to reduce cycle times: these include master protocols, adaptive trial design, enhanced segmentation of patients and disease, simulating protocol feasibility and use of AI and RWE for regulatory approvals (listed in Figure 15). These approaches provide a nuanced understanding of patients and their disease, and enable identifying high-responder sub-populations to improve development efficiency, the quality of research, and patient experience during clinical trials.

In summer 2020 we interviewed 19 R&D executives from biopharma companies (including some from our cohort) for Deloitte's report, *Bringing new therapies to patients: Transforming clinical development*, aimed at gaining a better understanding of the current adoption of these new approaches, their impact, and how they can be applied more broadly.

We found that some companies have been actively experimenting with these approaches, but that they have yet to be scaled up and used more broadly or in an integrated fashion. The portfolios of these companies further along the road to adopting transformative approaches are focused on oncology and rare diseases.

CASE STUDY 2

Matching patients to trials during the COVID-19 pandemic

Antidote Technologies, a digital patient engagement company, uses precision recruitment to match patients to the right clinical trial. Its proprietary platform structures and organises trial data from ClinicalTrials.gov into a patient-friendly, searchable format. Patients then use Antidote's search tool, Antidote MatchTM, to answer a few questions about their health, and the system automatically identifies clinical trials for which the patient could qualify. For sponsors with multiple trials in their programmes, Antidote offers multi-trial matching as a recruitment tool. This allows patients to match against several clinical trials from the same sponsor, increasing their chances of finding a trial and accelerating research for the sponsor.[7]

In March 2020, the company modified its search tool to match patients to clinical trials for compounds aimed at COVID-19 treatment and prevention. Antidote has reported that searches for clinical trials increased by 22 per cent in March 2020 compared to March 2019, which is related to how the health crisis changed digital engagement behaviors, and impacted clinical trial data, operations, and recruitment.[8]

CASE STUDY 3

Digital data flow across the clinical trial

A large biopharma company organised a hackathon to test the feasibility of using AI to automate the study start-up process with the aim of reducing trial cycle times and costs. The hackathon explored how AI could process and interpret data in unstructured documents (e.g. study protocol), identify discrepancies in manually entered trial data, and digitalise data elements in key documents so that they could be transferred to downstream systems without manual effort.[9]

Transformative approaches to drug development have the ability to reduce cycle times: these include master protocols, adaptive trial design, enhanced segmentation of patients and disease, simulating protocol feasibility and use of AI and RWE for regulatory approvals.

Figure 15. Transformative approaches to drug development

Adaptive trial design	Master protocols	Enhance segmentation of disease and patients	Simulating protocol feasibility	RWE for regulatory approvals
• Enables continuous learning and adjustments to condense cycle time and decrease the number of patients required to reach endpoints.	• Collaborative clinical studies for the simultaneous evaluation of multiple treatments for specific diseases or disease subtypes within the same trial structure.	• Combines scientific and real-world data to develop a nuanced understanding of a disease to identify novel endpoints relevant to specific patient subpopulations.	• Modelling and simulation can assess the impact of protocol decisions (e.g., inclusion and exclusion criteria) on addressable patient population.	**External control arms**
• Adaptive randomisation increases the probability of patients being assigned to more efficacious treatments arms or cohorts.	– **Basket trials:** A protocol employing a targeted therapy for multiple diseases.	• Clinical trials targeting narrower subpopulations require reduced sample sizes to reach endpoints and demonstrate statistical significance.	• Predict trial enrollment based on past site performance or the competitive trial landscape.	• Reduce the overall number of patients required for enrollment to accelerate development.
• Most widely adopted in oncology but use in rare diseases immunology, inflammatory, and neurology is steadily increasing.	– **Umbrella trials:** Use one protocol to study more than one targeted therapy for a single diseases.		• Few companies are developing algorithms to understand how recruitment time could change by modifying one or two inclusion exclusion criteria.	• Provide a better representation of the actual standard of care when the treatment landscape is dynamic or there is no standard of care.
	– **Platform trials:** A protocol employing multiple therapies for a single disease, with therapies allowed to enter/exit based on the decision algorithms.			**Label expansion**
				• Some companies have had success gaining new indications using RWE, saving the time and cost of running full clinical trials.

Source: Deloitte analysis.

# The COVID-19 experience: Sowing the seeds of change for the future

In 2020 the COVID-19 pandemic overwhelmed countries across the globe and significantly disrupted clinical trial operations. Despite these disruptions there were several 'silver linings' from the COVID-19 experience that have sown seeds of change for the future of R&D. The pandemic accelerated the adoption of digital technologies in clinical trials, and led to an extraordinary level of industry collaboration, wider application of transformative approaches (such as master protocols and adaptive trial design and the use of RWE), proving that it is possible to drastically reduce drug and vaccine development timelines. Moreover, the accelerated development of COVID-19 therapies and vaccines is expected to have a positive impact on the industry IRR (albeit not in 2020).

The COVID-19 pandemic has had a negative impact on cycle times for non-COVID trials

In March 2020, COVID-19 began to sweep across the globe, overwhelming most countries' healthcare systems. Operations at clinical trial sites were affected, due to staff shortages, mandatory lockdowns, and social distancing norms introduced to curtail the spread of the virus. Patients were unable or reluctant to travel and participate in trials owing to the risk of infection. Biopharma companies, clinical research organisations (CROs) and other research organisations were forced to shutdown trials, suspend enrolment, or delay planned study start-ups or completions.

According to GlobalData, between March and November 2020, COVID-19 affected an estimated 1,210 trials across the industry. A vast majority of these (66 per cent) had delayed starts or completions; and eight per cent were terminated (permanently stopped) or withdrawn (stopped before enrolling any patients). While all phases of trials were affected, 29 per cent of affected trials were in Phase III, which can impact asset launches and sales (Figure 16).

Figure 16. Impact of COVID-19 on trials across the industry, March-November 2020

Trials impacted by COVID-19 (type of impact)
Total # of impacted trials = 1210

Trials impacted by COVID-19 (by phase)
# of clinical trials impacted by COVID-19
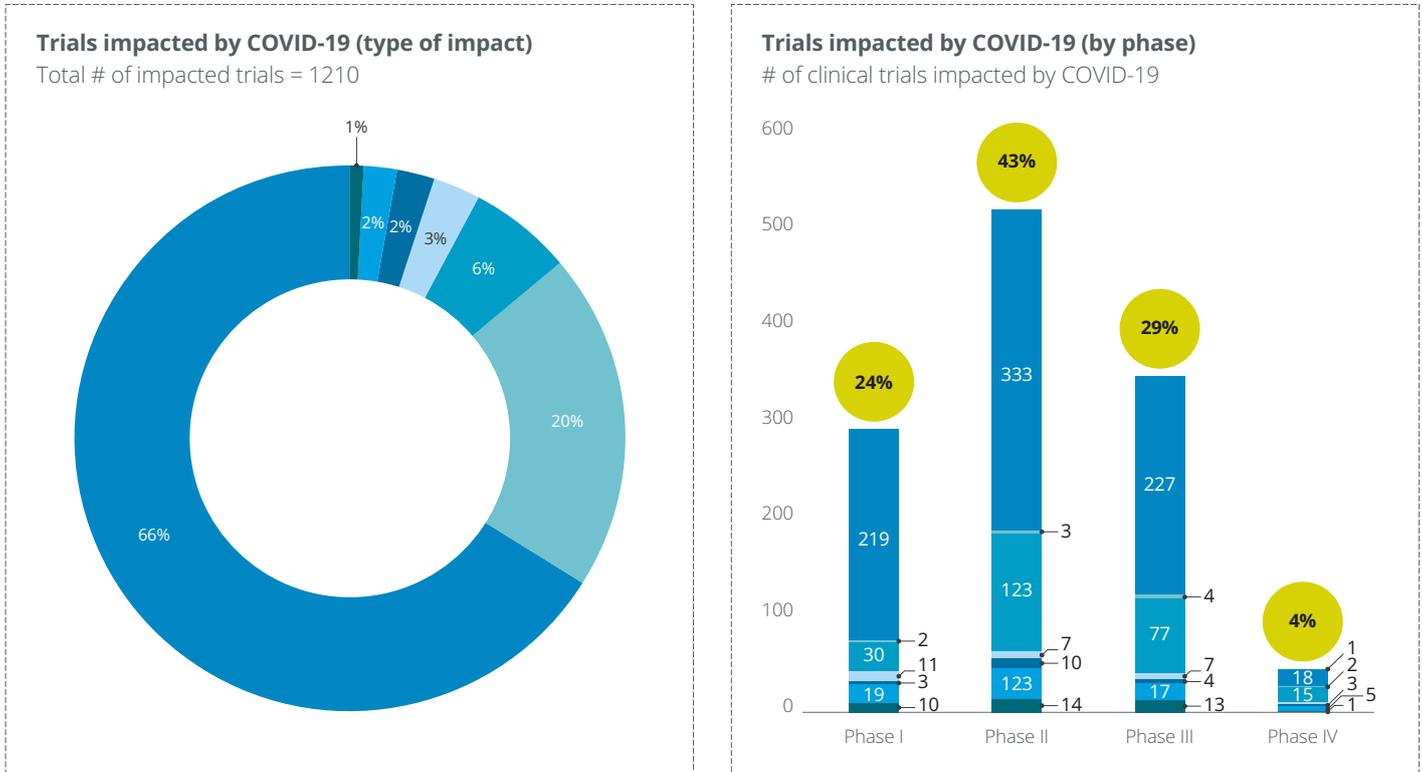
- ■ Disrupted ongoing expedited
- ■ Completed Early
- ■ Withdrawn
- ■ Suspended
- ■ Terminated
- ■ Disrupted ongoing with no impact on timelines
- ■ Disrupted ongoing delayed
- ● % of trials impacted by COVID-19 across phases

Types of COVID-impact:

- **Suspended trials:** Recruitment/enrollment stopped as a result of COVID-19, however, trials have the potential to start again.

- **Terminated trials:** Study stopped early as a result of COVID-19 and will not start again. Participants are no longer examined or treated.

- **Withdrawn trials:** Study stopped as a result of COVID-19 before enrolling its first patient.

- **Completed early:** Study ended normally, however, earlier than previously expected as a result of COVID-19.

- **Disrupted Ongoing trials:** Study is ongoing after temporary suspension or other type of COVID impact. Subcategories includes *trials delayed*, *trials expedited* owing to COVID-19 or *without impact on timelines*.

Source: GlobalData.

Figure 17. Clinical trials affected by COVID-19 across therapy areas
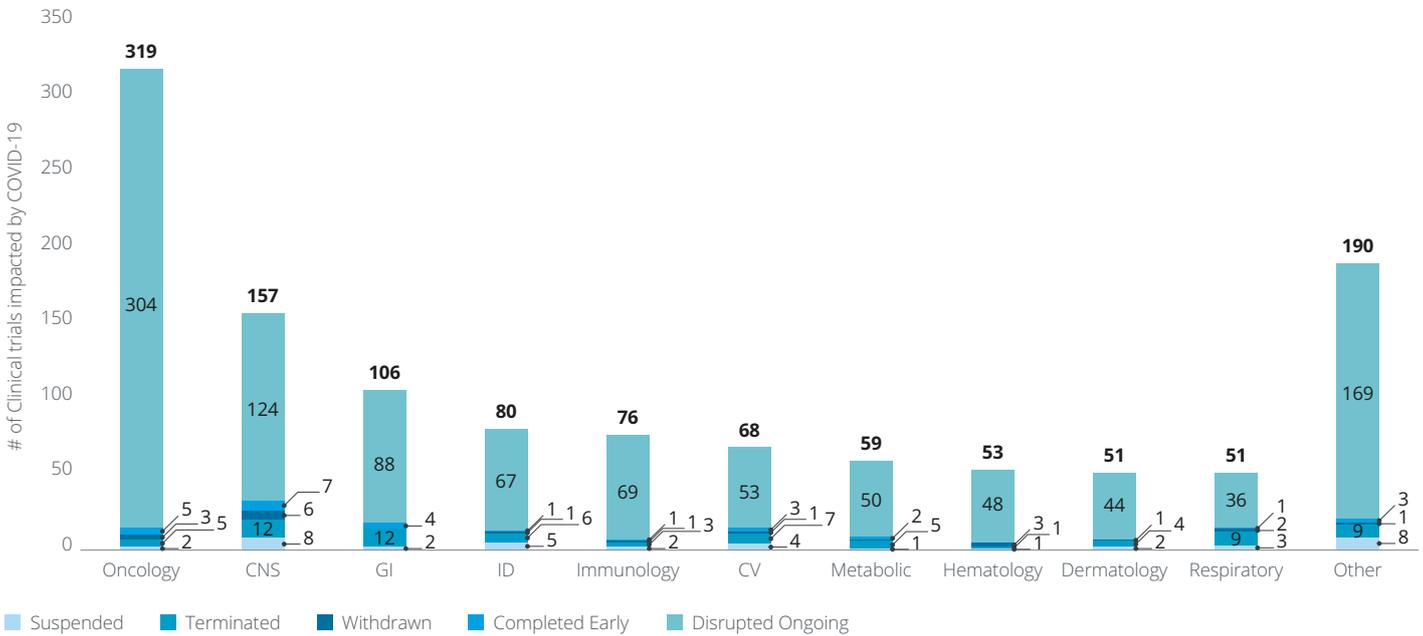
CNS = central nervous system, GI = gastrointestinal, ID = infectious disease, and CV = cardiovascular.
Source: GlobalData.

This disruption to clinical trials called for a re-imagining of traditional site-based development models. Many trials adopted hybrid study approaches, involving virtual/remote check-ins with participants, use of eConsent, mobile devices, apps to collect data, and delivering study products directly to patients. According to the Tufts Center for Drug Development, by November 2020, more than half of ongoing trials across the globe were using some remote or virtual support.[10] Most industry commentators expect this adoption of hybrid study approaches to be a stepping-stone to a broader industry transition towards decentralised clinical trials – where patient data is collected remotely or virtually and patients do not need to visit trial sites.

The impact of COVID-19 on trials varied across therapy areas (TA) (Figure 17). Oncology and CNS were the most affected, accounting for 40 per cent of all impacted trials. Complex trial protocols and difficulty with conducting remote assessments (patients needing to travel for infusions, tumour screening and diagnostic testing) limit the use of hybrid approaches for these TAs. Respiratory and dermatology trials were the least affected.

COVID-19 also elevated the discussion on the disproportionate impact of certain diseases on underserved populations and under-represented minority populations in clinical trials. In the US, as well as in many other countries, the disproportionate impact of COVID-19 on black and indigenous people of colour (BIPOC) and Latinx communities spurred greater interest in ensuring that the make-up of clinical trial participants for COVID-19 vaccines and therapies match the prevalence of disease across racial and ethnic populations.[11,12] Some companies like Pfizer and Moderna worked to achieve greater diversity in their COVID-19 vaccine trials, with Moderna even slowing down recruitment to enrol more racial and ethnic minorities in the US.[13] As indicated in our report *Intelligent clinical trials,* decentralised or hybrid trials can help recruit more representative study populations (across gender, ethnicity, geography and income levels), providing the data needed to understand efficacy and safety for the intended populations that are likely to use the treatments being tested (see sidebar: Improving diversity in clinical trials).

Many trials adopted hybrid study approaches, involving virtual/remote check-ins with participants, use of eConsent, mobile devices, apps to collect data, and delivering study products directly to patients.

Looking at the top 20 biopharma companies by R&D spend, COVID-19 is expected to delay a few asset launches, but the net revenue impact is likely minimal

We analysed the impact of COVID-19 between March to November 2020 on development timelines for 2020 pipeline assets of the top 20 biopharma companies by R&D spend. Our analysis shows that, across these companies, 25 Phase III trials faced temporary disruptions and delays that could have affected asset launches (Figure 18). Yet, the forecasts for only two companies showed that expected launch delays would result in a total estimated sales impact of $308 million (with no expected impact on peak sales).

In addition, four trials were discontinued owing to COVID-19 resulting in a decline by an estimated $235 million in average peak sales for three of these companies over a 20-year period.

Our research suggests that pre-pandemic investments in analytics, AI and digitalising trial operations enabled some of the top 20 companies by R&D spend to adapt quickly and keep trials moving (see case study 4), without affecting anticipated launch timing. Others invested quickly to digitalise their trial operations and run trials remotely, to reduce the impact of COVID-19 on submission timelines.

Over the years much has been said about the fact that clinical trials do not reflect the diversity of populations that drugs under development are intended to treat.

Figure 18. Phase III trials of the top 20 biopharma companies by R&D spend affected by COVID-19

- Suspended
- Terminated
- Withdrawn
- Completed early
- Ongoing Disrupted
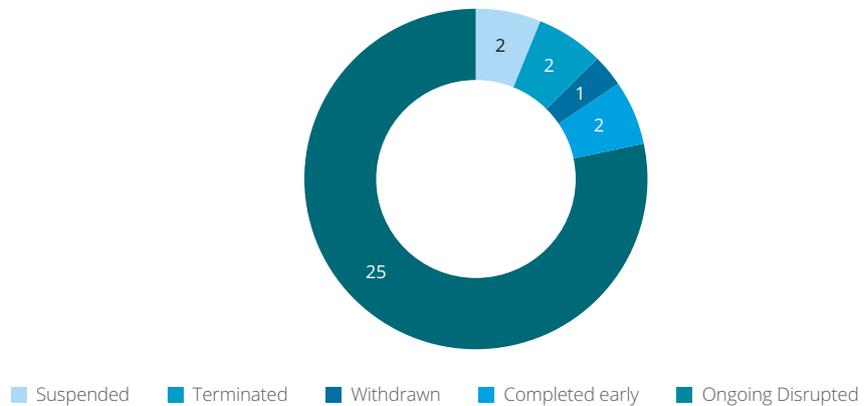
Source: Global Data.

Improving diversity in clinical trials

Over the years much has been said about the fact that clinical trials do not reflect the diversity of populations that drugs under development are intended to treat. In the US, underrepresented populations are more likely to suffer from cancer, diabetes and heart disease and could benefit the most from new treatments. While close to 40 per cent of the US population belongs to a racial and ethnic minority, most participants in clinical trials are White Americans. According to the US FDA, White Americans accounted for 78 per cent of participants at US sites between 2015 and 2019.[14,15] In the UK, type 2 diabetes disproportionately impacts South Asians whose mean involvement in clinical trials was found to be 5.5 per cent, despite representing 11.2 per cent of the UK type 2 diabetes population.[16]

Existing clinical trial site infrastructure can create barriers for underrepresented populations to participate in clinical trials. For example, most clinical trials are conducted at academic medical centres that do not serve underrepresented populations, affecting the ability to recruit a diversified participant pool. Further, underrepresented populations can be disproportionately impacted by the time required and the financial consequences of clinical trial participation, such as long travel distances to study sites, limited flexibility at work, child-care concerns, and health care costs.[17] Other barriers include lack of understanding of the value of research, fear and stigma about participating, and poor engagement/communication between clinical researchers and participants.

Decentralisation of trials, bringing trials to a patient's home, can help overcome these challenges and may provide a way to improve diversity among participants. Through the use of telemedicine, digital technologies to remotely capture patient data and drug deliveries direct to patients, these trials eliminate the burden on patients of travelling to sites or taking time away from work or childcare. Trial patient matching algorithms coupled with apps (such as those for eConsent) could increase the efficiency and speed of identifying and recruiting a more diversified study population irrespective of geographical location. Furthermore, the use of wearable and mobile technologies to monitor and support patients could improve engagement and communication between participants and researchers, improving the overall trial experience and trial retention rates.

CASE STUDY 4

Novartis uses advanced analytic and digital technologies to minimise trial disruptions

Past investments by Novartis in advanced analytics, AI and digital technologies enabled the company to react rapidly and flexibly to COVID-19, limiting the impact of the pandemic on expected submission timelines.[18,19,20]

In 2018, Novartis launched its Nerve Live platform that uses predictive analytics and AI for site selection, modelling enrolment scenarios, drug supply and resource requirement planning (such as staffing and time commitments). The platform also includes SENSE, a module that collates real-time updates on all ongoing trials, and Resource Cockpit, which enables prediction and optimisation of resource allocation for clinical trials.[21]

Through the pandemic, development teams used Nerve Live for real time visibility into trial activity to predict where disruptions were likely to happen and intervene to mitigate them.[22] Leveraging digital technologies, the company also undertook virtual safety assessments and conducted 35,000 remote monitoring visits in 2020. In December 2020, Novartis reported that COVID-19 was likely to cause minimum disruptions (less than 3 months) for the majority of its regulatory submissions through 2025.[23]

Despite disruptions, there are silver linings from the COVID-19 experience

The COVID-19 pandemic showed that it is possible for the industry to adapt at a scale that many believed would take years to become a reality. The pandemic accelerated the adoption of digital technologies in clinical trials, and new COVID vaccines and therapies were developed in record time through extraordinary collaboration and wider use of transformative approaches (such as master protocols and adaptive trial design).

Scaling the use of digital technologies in trial operations

Companies had been experimenting with digital technologies for years, but the inherent risky nature of drug development made them reluctant to upscale digital technology use and disrupt how development has been done 'traditionally'. The pandemic created a situation that forced the adoption and de-risked the use of digital technologies for remote patient monitoring, virtual check-ins, recruitment and other purposes.[24]

In a November 2020 survey of CROs, biopharma and MedTech companies, 67 per cent of respondents reported that their organisations had incorporated remote data collection into their trials, through use of patient apps, including electronic patient-reported outcomes (ePRO), and wearables/devices.[25] The benefits included patient convenience (64 per cent), real-time data and better insights (52 per cent), as well as time and resource savings for site staff (45 per cent) and sponsors (28 per cent).[26] Such efficiencies and benefits from the use of digital technologies have increased interest among business leaders and clinical staff to adopt these technologies on a more routine basis in trial operations. In fact, 76 per cent of respondents from the same survey indicated that the pandemic had accelerated the adoption of decentralised approaches to running clinical trials.[27]

New vaccines and therapies were brought to market in record time through extraordinary collaboration and use of transformative approaches

The unparalleled health care and economic crisis created by the pandemic necessitated an equally unparalleled response from the life sciences industry. It is truly remarkable to see how biopharma companies have risen to the challenge by investing and developing treatments and vaccines in record time (see sidebar: Industry moved quickly to bring novel COVID-19 vaccines to market). The pandemic also provided an opportunity to accelerate the development of new technologies (such as mRNA and adenoviral vector technologies) to quickly address a global unmet need.

> ❝Eli Lilly learned how to conduct its clinical research virtually. Enrolment with digital support was faster than expected and patient dropout rates were lower than expected. We plan to make permanent virtual clinical trials featuring remote monitoring and digital interactions with trial sites.❞

David Ricks, CEO, Eli Lilly.[28]

## Industry moved quickly to bring COVID-19 vaccines to market

COVID-19 vaccines were brought to market in less than a year compared to the traditional 10 to 15-year development timeline. Timely regulatory action (see sidebar: Regulatory flexibility during the pandemic), stakeholder collaboration, and significant public and private funding enabled companies to run development and manufacturing activities in parallel, de-risking the entire vaccine development process.

The race to develop COVID-19 vaccines began with the rapid sequencing and public release of the SARS-CoV-2 genome in January 2020. Decades of research and previous advancements in mRNA vaccine technology (initially targeted at developing cancer vaccines) enabled companies using these platforms to create vaccine candidates and launch pre-clinical studies within weeks. Government and private funders poured in billions into promising vaccine development programmes (mRNA and others) even pre-ordering vaccine doses, thereby de-risking development. For instance, the US government placed a pre-order for 100 million doses of the Pfizer vaccine in July 2020, before Phase III clinical data was available and the UK pre-ordered 100 million doses of Oxford-AZ vaccine. [29,30] Vaccine manufacturers also leveraged adaptive seamless trial designs (that combined phases of development), started manufacturing in advance of approvals, and undertook rolling data submissions (i.e. submitting data to regulators as soon as it was available) that reduced the regulatory review time. By early December 2020, Pfizer's mRNA COVID-19 vaccine was approved for emergency use in the US and UK[31] while the Oxford-AZ vaccine was approved for emergency use in the UK at the end of December 2020 (Figure 19).[32]

Figure 19. Development timelines for the Pfizer m-RNA vaccine and Oxford-AZ vaccine
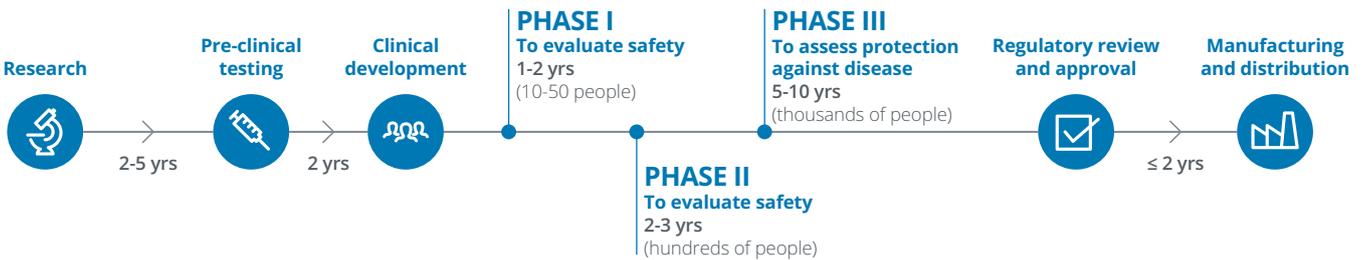
The traditional development pathway takes **on average over 10 years** to get a vaccine licensed. Pfizer-BioNTech's mRNA COVID-19 vaccine was bought to market in a year.

1. COVID-19 vaccine development: Pfizer-BioNTech mRNA vaccine
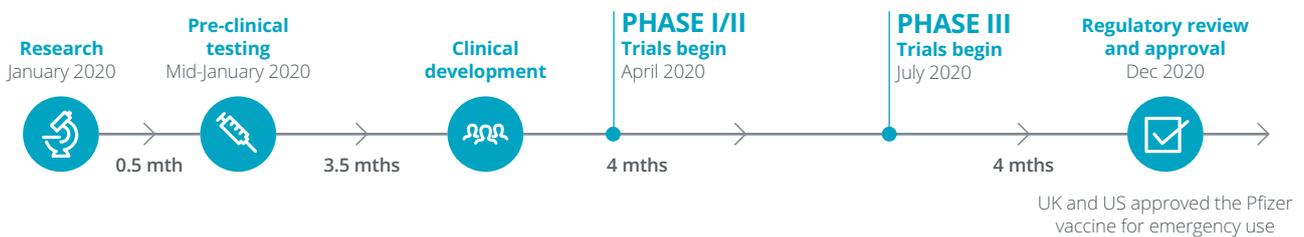
2. Oxford-AstraZeneca COVID-19 vaccine development timeline
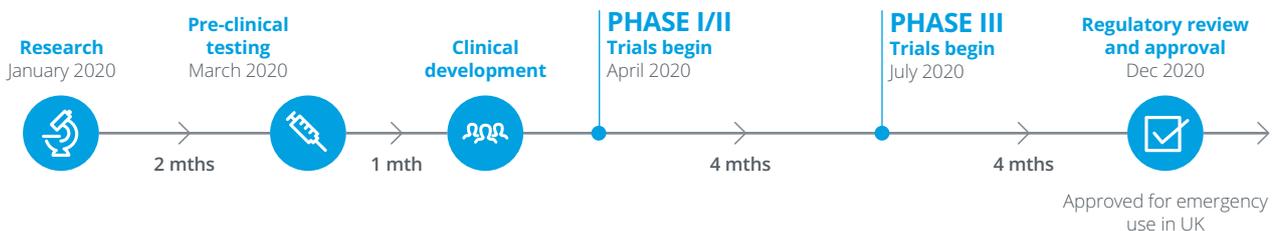
Source: Deloitte analysis

Extraordinary levels of collaboration
The urgency to bring new vaccines and therapies to market led to an extraordinary level of collaboration to share data and pool resources, expediting development timelines. Alliances among traditional competitors, industry stakeholders and public-private partnerships enabled sharing of trade secrets and intellectual property in order to meet a common goal. For example:

- Through the COVID-19 R&D Alliance, several biopharma companies came together to share data from COVID-19 related trials and created a common mechanism to screen the most promising vaccines and therapeutic candidates.[33] Members capitalised on clinical trial data from their competitors to derive insights, inform trial design, and minimise unnecessary duplication of research efforts (see sidebar: The COVID Research and Development Alliance).

- Public private partnerships such as the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) coordinated by the Foundation for the National Institute of Health brought together government agencies, regulators, biopharma companies and non-profit organisations to standardise pre-clinical evaluation methods, evaluate potential therapeutic candidates for development, and optimise sharing and use of clinical trial infrastructure. ACTIV has also designed and launched several platform clinical trials to test prioritised COVID-19 therapies including immune-modulators, antivirals, neutralising antibodies and anti-thrombotics.[34]

- Competitors shared resources and capabilities more openly than before; the CoVIg-19 Plasma Alliance is one such example, where traditional competitors collaborated on plasma collection, development, and manufacturing of convalescent plasma solution for COVID-19 patients.[35]

- In the EU, the Corona Accelerated R&D in Europe (CARE) project created a consortium of 37 academic institutions, pharmaceutical companies and non-profit research organisations for drug repurposing and development of antibody therapies against the virus. The project received € 75.8 billion in funding from members of the consortium.[36]

The COVID-19 Research and Development Alliance

At the onset of the pandemic, R&D leaders of at least seven large biopharma companies formed the COVID R&D Alliance to cut red tape and combine and leverage their resources to respond quickly to the pandemic.[37] The alliance has now grown to include 21 biopharma companies and two venture capital firms.[38] Some of the alliance's achievements include:

- Created a centralised screening mechanism to evaluate agents not only from their own pipelines but also from those submitted from the field for antiviral activity. By August 2020, the alliance had evaluated over 1,900 pre-clinical candidates and had started to link promising ones with potential funders.[39]

- Enabled researchers to share summary-level statistics using TransCelerate's DataCelerate® platform.[40]

- Partnered with Quantum Leap Healthcare Collaborative, the consortium that setup the I-SPY adaptive trial platform to test therapies for late-stage respiratory failure owing to COVID-19.[41]

- In November 2020, the alliance also launched its own master protocol trial, COMMUNITY, (COVID-19 Multiple Agents and Modulators Unified Industry Members), that is used by members to test novel immuno-modulatory therapies against COVID-19.[42]

The alliance will continue its work in 2021 to build a secure master repository of de-identified clinical trial data sourced by members and work towards enabling real-time sharing of patient-level trial data.

Alliances among traditional competitors, industry stakeholders and public-private partnerships enabled sharing of trade secrets and intellectual property in order to meet a common goal.

Transformative approaches to clinical development became more widely adopted

Transformative approaches, especially master protocols, and adaptive trial designs were used to accelerate the pace of development. While these approaches have been around for decades, their application had been mostly limited to oncology and rare disease. The sense of urgency created by the pandemic led to wider use of these approaches, increasing the potential for greater acceptance and adoption by leaders in the industry.[43]

During the pandemic, master protocols emerged as critical tools for public health agencies and other industry stakeholders to collaborate in testing the safety and effectiveness of repurposed drugs and new therapies. Several large-scale master protocol trials were launched, many of which produced high-quality actionable results.[44] Some notable examples include:

- The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial launched in March 2020 in the UK by the National Institute of Health Research (NIHR) and University of Oxford demonstrated the benefits of dexamethasone and tocilizumab to treat hospitalised COVID-19 patients and proved that hydroxychloroquine and azithromycin provided little benefit as COVID-19 therapies.[45] The trial also demonstrated HIV treatments, lopinavir and ritonavir, were ineffective against the virus. RECOVERY recently began recruiting participants in Indonesia and Nepal to test aspirin and colchicine as potential low-cost treatments against COVID-19.[46]

- SOLIDARITY, the WHO's master protocol to test repurposed drugs against COVID-19, enrolled patients from over 30 countries and found hydroxychloroquine, lopinavir and ritonavir, and interferon had little or no effect on overall mortality, the initiation of ventilation or the length of hospital stay.[47]

- Existing master protocols such as REMP-CAP for pneumonia and I-SPY for breast cancer were repurposed for COVID-19, further proving the adaptability and benefit of master protocols.[48]

Adaptive trial designs were used to test the efficacy of repurposed therapies to treat patients hospitalised with COVID-19 symptoms. In April 2020, results from the Adaptive COVID-19 Treatments Trials in the US validated the clinical benefits of remdesivir to treat hospitalised COVID-19 patients. Companies also leveraged adaptive trial designs to expedite patient access to novel lifesaving COVID-19 treatments. For instance, Regeneron Pharmaceuticals made use of a seamless Phase II/III trials design to move its antibody therapy rapidly through development phases, and receive emergency use authorisation in the US.[49]

During the pandemic, master protocols emerged as critical tools for public health agencies and other industry stakeholders to collaborate in testing the safety and effectiveness of repurposed drugs and new therapies.

Regulatory flexibility during the pandemic

During the pandemic, regulators developed and released flexible guidance that enabled companies to run trials remotely, and created new mechanisms or activated existing ones to expedite development, review and approval of potential therapies and vaccines.

In Europe:

- In early February 2020, the European Medicines Agency (EMA) activated its emerging health threats plan to expedite the development of vaccines and treatments for COVID-19. This plan detailed the principles under which the agency should operate during the pandemic and provided a framework for coordinating scientific and regulatory activities throughout Member States. [50]

- To mitigate the disruption to regular clinical trial activity, in March 2020 the EMA released its first set of recommendations for sponsors to manage clinical trial conduct during the pandemic, which it has continued to update. It included recommendations on adjusting monitoring activities, managing and documenting protocol deviations and investigational product distribution and data verification under social distancing.

- The EMA also convened a COVID-19 EMA Taskforce to provide scientific advice and evaluate COVID-19 related products. It also introduced initiatives to accelerate the development of treatments and vaccines, including rapid scientific advice, rolling reviews, accelerated marketing authorisations and compassionate use programmes.[51]

In the US:

- The FDA released and continued to update guidance on the use of electronic informed consent, remote monitoring, remote clinical outcome assessments and capturing data on protocol and process deviations.[52,53]

- In March 2020, the US FDA launched the Coronavirus Treatment Acceleration Program (CTAP) that enabled sponsors to seek and receive timely guidance from review divisions and SMEs on product development and trial design. In less than a year the CTAP has reviewed more than 440 trials related to COVID therapies and approved several treatments and three vaccines for COVID-19 on an emergency use basis.[54,55] The US FDA also released two new guidance documents to speed up pre-clinical and clinical studies for COVID-19.[56]

- This was all in addition to approving 53 new drugs in 2020, the second highest number in the past five years.[57]

The proactivity of regulators during the COVID-19 crisis proved that it is possible to balance rapid innovation with real-time regulatory change and bring greater agility in regulatory approaches and processes. Digitalising the regulatory approval process and data exchange between companies and regulators could enable efficient and faster review and access to new therapies.

Regulators could also use the experience gained during the pandemic from the use of remote patient monitoring tools, RWE, and advanced analytics, and working in collaboration with the industry to build a blueprint for future regulation.

Expanded focus on increasing of the utility of RWD/E for R&D

The pandemic also bought together stakeholders to collaborate on increasing the utility of RWD/E. Since the beginning of the pandemic, data scientists and researchers were engaged in efforts to capture and analyse RWD to understand the nature of the disease and the efficacy of drugs to manage COVID-19 patients. The Reagan-Udall Foundation's COVID-19 Evidence Accelerator brought together major data organisations, the FDA and academic researchers to advance methods to convert RWD into actionable COVID-19 insights. The shared learning environment enabled members to conduct parallel analyses, share and compare results, and solve challenges on RWD standardisation and interoperability. The accelerator is also developing a set of common data elements that can be embedded uniformly into data collection efforts to allow for rapid aggregation and analysis, and this approach could even be applied to other disease areas.[58] Such accelerators could be invaluable for advancing the science of RWD/E and building the confidence in the rigor of RWE for regulatory and healthcare decision making.[59]

Biopharma companies also used RWD to understand usage patterns of COVID therapies and investigate the efficacy of therapies in treating populations more vulnerable to the disease. For instance, after receiving emergency use authorisation for remdesivir, Gilead Sciences analysed hospital data on the drug's usage. This analysis showed the drug was being reserved for the treatment of the sickest, mechanically ventilated patients (owing to supply shortages), even though clinical trial data suggested that the drug performed best when used earlier. The company took these findings to the NIH that incorporated it into guidelines on remdesivir use to maximise the drug's benefit. [60] The company also conducted a retrospective analysis of hospital data from patients with severe COVID infection belonging to various racial and ethnic groups who were being treated with remdesivir and compared it to Phase III trial results. The analysis revealed that patients from racial or ethnic groups who received the drug had similar clinical outcomes as the overall patient population.[61]

Investment in COVID-19 vaccines and therapies could potentially uplift overall industry IRR while leading in the future to a greater focus on preventative therapies

Given the scale of the pandemic, companies developing COVID -19 treatments and vaccines are likely to see robust returns on their investments and efforts. By mid-February 2021, six of the top 20 biopharma companies by R&D spend had received conditional approval and/or marketed COVID-19 therapies and vaccines in the US, the UK and the rest of Europe. Some of these companies released estimates for vaccine and therapy sales in 2021. For instance, Pfizer predicts $26 billion from sales of its coronavirus vaccine doses and Gilead expects up to $3 billion from sales of Veklury (remdesivir) in calendar year 2021.[62,63] We estimate average forecast peak sales of five conditionally approved COVID-19 therapies and vaccines (as of mid-February 2021) to be $3.4 billion in 2021, compared to the average forecast peak sales of $410 million per asset for the entire portfolio in development by the top 20 biopharma companies by R&D spend in our 2020 analysis period. This is only a sample of COVID-19 therapies and vaccines, and other assets still in development may also contribute to an uplift in overall industry revenues and IRR.

The pandemic may also lead to future R&D portfolios pivoting towards a greater focus on infectious disease. In 2020, we found that the vaccine pipeline for the top 20 biopharma companies by R&D spend was primarily focused on infectious diseases (including dengue, HIV and Ebola) and that the late-stage pipeline analysis for these companies indicates that revenues from vaccines are expected to reach $11.0 billion by 2030 as compared to $0.1 billion in 2020.

In Deloitte's Future of Health™ vision, we predict that preventive therapies, including vaccines, will become an increasingly important revenue source for biopharma, in addition to an important tool for public health strategies. Advances in vaccine development and manufacturing technologies such as mRNA vaccine platforms could play an important role in this future. The 'plug-and-play' nature of mRNA vaccine technology, which unlike traditional vaccines does not require unique infrastructure for each development programme, could expedite the creation of vaccine candidates against viral and bacterial pathogens. Leading companies in the mRNA vaccine space are already developing vaccines for infectious disease-causing pathogens, including influenza, HIV, tuberculosis and cytomegalovirus. mRNA vaccines that boost the body's ability to recognise and kill tumour cells are also being tested against 11 specific cancer types. Given the volume of unmet need that such vaccines could address, they are likely to contribute to an increasing share of biopharma revenues over the next two decades.[64]

Given the scale of the pandemic, companies developing COVID-19 treatments and vaccines are likely to see robust returns on their investments and efforts. By mid-February 2021, six of the top 20 biopharma companies by R&D spend had received conditional approval and/or marketed COVID-19 therapies and vaccines in US, the UK and the rest of Europe.

What's next for biopharma R&D and how should companies prepare?

The pandemic has sown seeds of change and accelerated the shift towards a more productive future for drug development. Nurturing these seeds will require companies to continue to invest in and operationalise technology, data science, collaboration, and transformative approaches.

Post-pandemic we predict an acceleration towards a data-driven future for R&D (for more see our *Predicting the future of health care and life sciences in 2025* report) in which new technologies and extensive use of transformative approaches could reverse the declining trend in IRR. This shift towards a new future of R&D requires four enablers: harmonised regulatory approaches and pathways with increased flexibility to expedite approval of novel therapies; democratising health care data to make it fluid, secure and usable; creating a digitally literate workforce with cognitive, analytical and data science skillsets; and the emergence of new business and payment models.[65] We believe that by 2025 the following enablers will impact R&D, including reducing costs and improving likelihood of success:

- Digital platforms, AI and access to RWD generated through partnerships with health care organisations, academia, digital tech companies and patient groups will accelerate R&D.

- Deep learning and other AI technologies applied to multiple data sets will improve the accuracy of drug discovery, delivering more precise therapeutic candidates.

- Transformative approaches such as master protocols, adaptive trials and use of RWE for regulatory submissions will be used at scale to cut development timelines and improve the quality of research.

- Data science techniques and AI applied to RWD will power trial enrichment strategies to and help design patient-centric trials design, define digital endpoints and improve the diversity of trial participants.

- Technology and rich data visualisation tools, including digital twins, will be employed across the study life cycle to automate repetitive tasks and simulate trials.

- The use of virtual/decentralised trials that employ apps, wearables and e-consent for faster recruitment, enrolment, and remote monitoring of patients will be commonplace across the industry.

- RWE will be used by regulators to support their decision making, including label expansions and revisions.

Preparing for the future will require companies to continue the momentum of collaboration built up during the pandemic, expand the use of digital technologies to run decentralised trials, and use transformative approaches to expedite drug development. Attracting and retaining data science talent will also be crucial.

Continue the collaboration momentum
The pandemic has shown that it is possible to break down traditional barriers to collaboration and gain meaningful benefits from doing so. Alliances, such as the COVID-19 R&D Alliance, enabled pre-competitive data sharing and pooling of resources to accelerate R&D. Companies should continue, expand or adapt successful collaborations formed during the pandemic. Pre-competitive data sharing could be applied to understand disease, share insights, and create master protocols in areas of high unmet need, such as Alzheimer's, HIV, and infectious and rare diseases.

Further, collaboration with regulators could enable more consistent and interconnected approaches to regulation globally. Some large pharma companies have come together to build a cloud platform for real-time, secure and rolling exchange of data between sponsors and the US FDA. Such a platform could potentially streamline the application, submission and assessment processes for new drugs and enable submitting data to multiple regulators in parallel.[66] Expanding regulatory pathways with increased flexibility and transparency could help to optimise access to new and safe therapies.

Decentralise and digitalise trials
While COVID-19 jump-started a digital revolution in clinical trials, much more sustained efforts are needed to accelerate the shift to sustained use of decentralised development models. Companies should craft a clear vision about their use of digital technology, allocate teams and resources for this purpose and build partnerships/alliances with digital technology vendors and service providers. Proactive engagement with regulators will also be important for how hybrid trial approaches and digital technologies can be incorporated into more routine use after the pandemic.

Expand use of transformative approaches

Companies should build towards a future where transformative approaches can be applied on a more routine basis. This may require widespread sharing of experiences and lessons from the use of master protocols, adaptive trials and other approaches, in order to build confidence in these approaches. Some such efforts are already underway. The Clinical Trials Transformation Initiative (CTTI) and the Duke-Margolis Center for Health Policy have convened investigators from COVID-19 master protocol trials to share information about their experiences in the fast-paced pandemic environment.[67]

Leaders should encourage development teams to experiment and consider where and when transformative approaches could be applied, especially in areas of high unmet need. This will require investment in technology infrastructure (such as RWE platforms and AI) to increase data utility and interoperability, and also data science talent to apply these approaches. Working with multi-stakeholders to build an ecosystem to collate data would assist in expanding access to high-quality research-grade data (for more information read our paper on *Bringing new therapies to market: Transforming clinical development*).

Acquire and retain data science talent

A diverse and digitally literate workforce will be critical for the future. This should include cognitive and analytical skillsets, as well as having digitally savvy leaders at all levels and AI-friendly, tech-savvy boards who recognise the importance of embracing new ways of working and robust change management skills. Data science talent will be crucial to combine and analyse data from disparate sources to accelerate drug discovery, increase trial efficiency, and support new approval pathways and reimbursement mechanisms. Companies should re-imagine future roles in data science and build a tailored human resource strategy to attract and retain data science talent, with talent acquisition processes to target data scientists with necessary skillsets. Once on board, data scientists should be provided with visibility into the impact and results from their work, recognition for their accomplishments, and career progression opportunities. Companies should also provide existing employees with opportunities to improve their data literacy, in order to understand the value of data or build data science and analytics skillsets.

Companies should re-imagine future roles in data science and build a tailored human resource strategy to attract and retain data science talent, with talent acquisition processes to target data scientists with necessary skillsets.

Methodology

Since 2010, our *Measuring the return from pharmaceutical innovation* series has focused on the projected returns from the late-stage pipelines of a cohort of the 12 largest biopharma companies by 2009 R&D spend. Our five most recent reports also include an extension cohort of four mid-to-large cap companies with analysis back dated to 2013. Throughout our analysis, we have used these two cohorts as a proxy to measure the industry's ability to balance initial capital outlay with the cash inflows biopharma companies are projected to receive as a result of this investment. Over the past few years, however, we have seen a convergence in the performance of our original and extension cohorts and this year we are combining the two cohorts to form a 'combined cohort'.

Our consistent and objective methodology focuses on each company's late stage pipeline (assets that are filed, in Phase III or Phase II with breakthrough therapy designation as of 30th April each year) and measures performance across the original and extension cohorts. We use two inputs to calculate the Internal Rate of Return (IRR): the total spend incurred bringing assets to launch (based on publicly available information from audited annual reports or readily available from third-party data providers) and an estimate of the future revenue generated from the launch of these assets.

As assets are approved, forecast revenues move from the late-stage pipeline into the commercial portfolio, moving out of scope of our analysis and decreasing the value of the late-stage pipeline. The graphic below illustrates our methodology, showing both the static year-on-year and dynamic (three-year rolling average) measures of R&D returns.

**Late-stage pipeline static IRR and drivers of change in IRR methodology**

Basket
of assets
for which
predicted
returns are
measured

Static IRR:
Snapchat calculation
based on investment
costs and expected
returns

Discovery | Preclinical | Phase I | Phase II | Phase III | Launch | 21 year sales forecast
(from external supplier)

+ submitted
for approval

Transition of new assets
from earlier phases,
in-licenced, acquired

Existing assets
Sales forecast
up/down

Dynamic IRR:
Illustrates the impact
on underlying levers
on changes in
IRR over time

Forecast sales from
terminated assets fall out

Forecast sales from
approved and launched
assets fall out

Source: Deloitte LLP, 2021.

Importantly, it should be noted that we are continually working to improve the methodology and modelling underpinning this analysis. This year there has been an improvement in the methodology used by GlobalData to obtain phase transition success rates which in turn has improved our methodology for risk-adjusting cash flows. Therefore, 2019 numbers have been re-adjusted and re-stated to allow for the analysis of the combined cohort and specifically the comparison with 2020.

As the overall declining trend seen since 2010 remains the same numbers referring to years prior to 2019 remain as stated in our 2019 report which were obtained with the best available information at the time of performing the analysis.

Appendix

Figure 20. Three-year rolling average returns on late-stage portfolio, 2013-20 – combined cohort
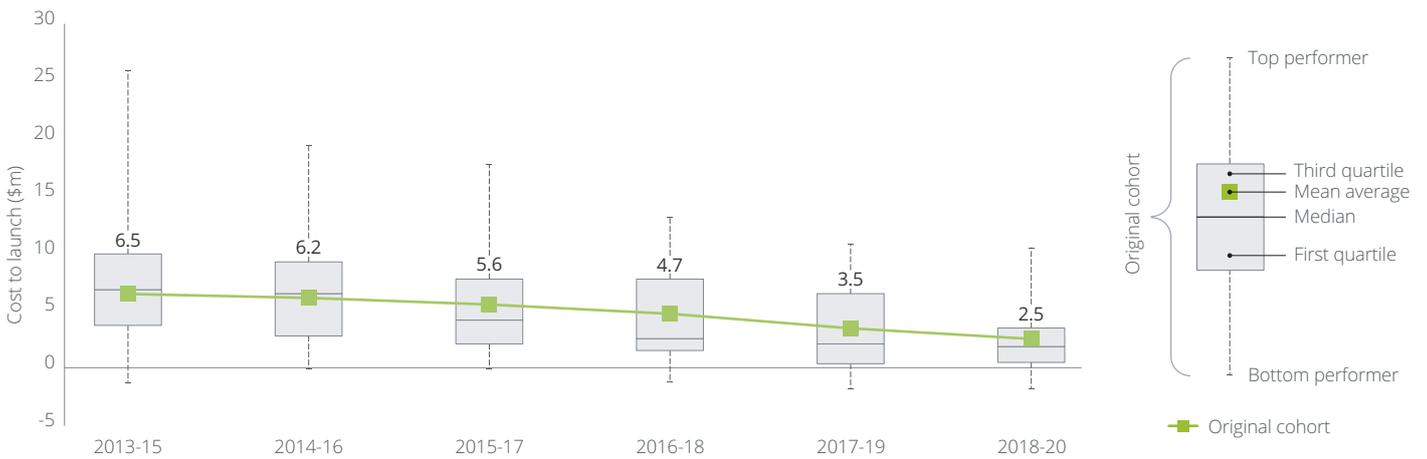

Note: 2019 numbers have been restated. For more information, see Methodology.
Source: Deloitte LLP, 2021.

Figure 21. Drivers of change in IRR. 2010-20 – original cohort (top); 2013-20 – extension cohort (bottom)
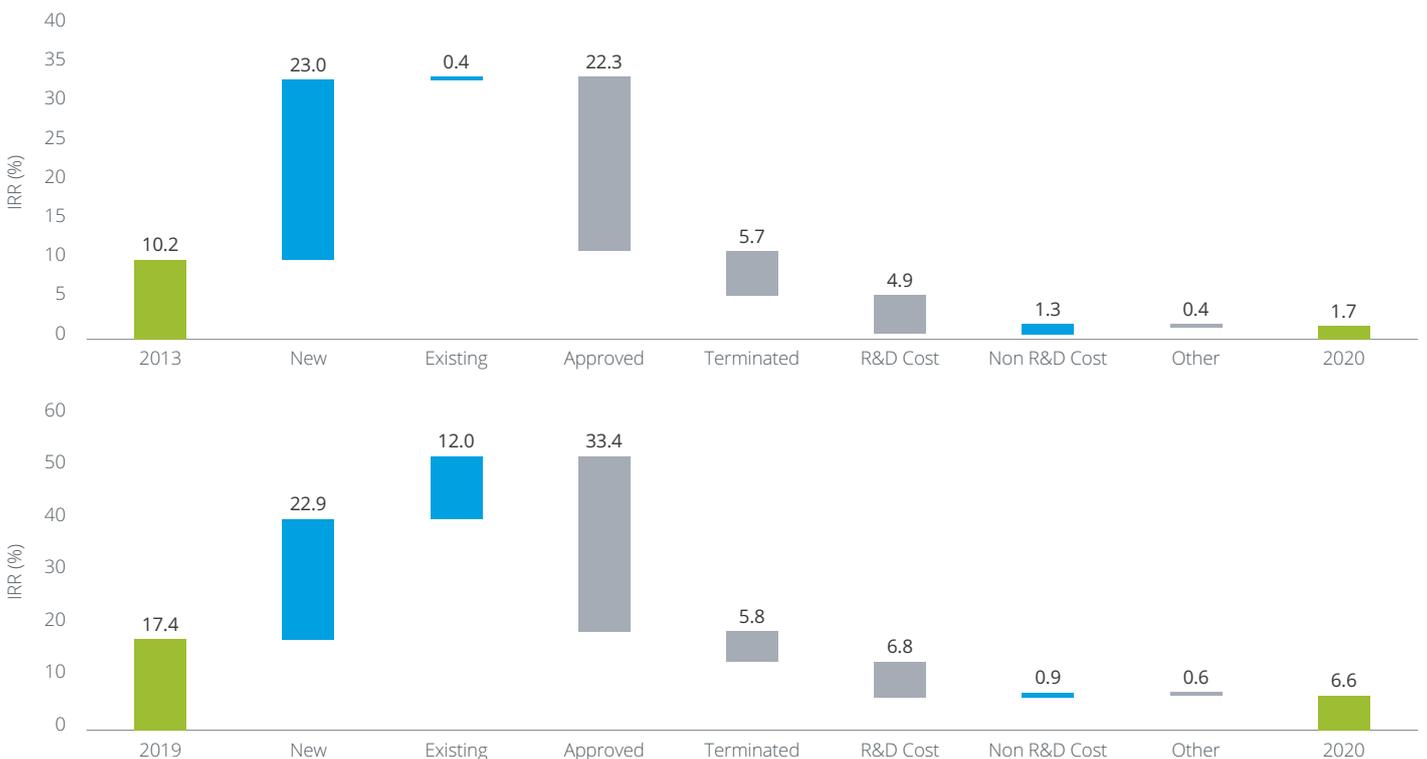

Note: 2019 numbers have been restated. For more information, see Methodology.
Source: Deloitte LLP, 2021.

Figure 22. Year-on-year drivers of change in IRR, 2013-20 – combined cohort
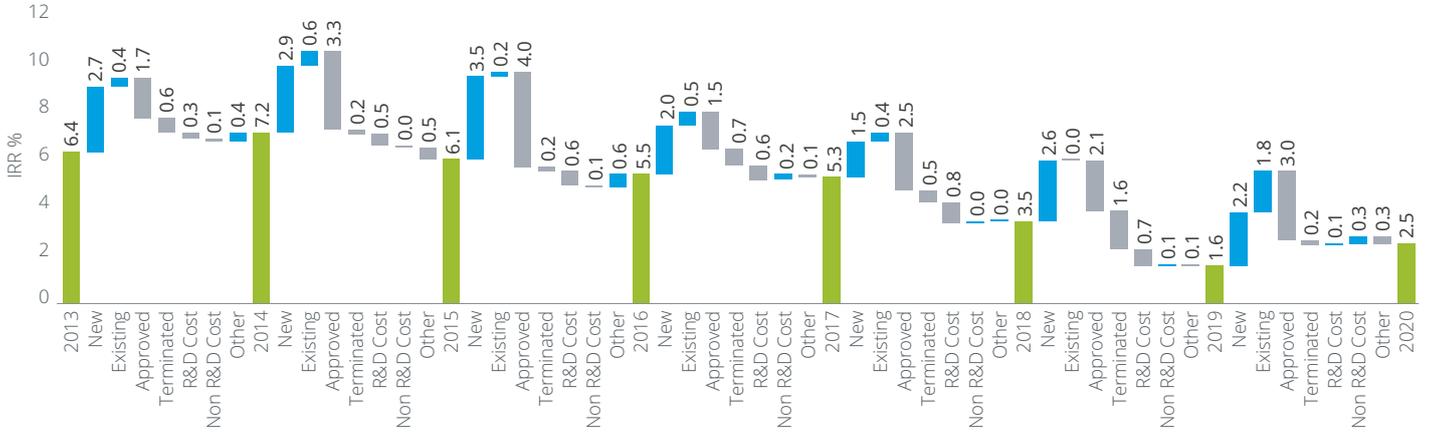
Note: 2019 numbers have been restated. For more information, see Methodology.

Source: Deloitte LLP, 2021.

Figure 23. Three-year rolling average R&D cost to develop a compound from discovery to launch, 2013-20 – combined cohort
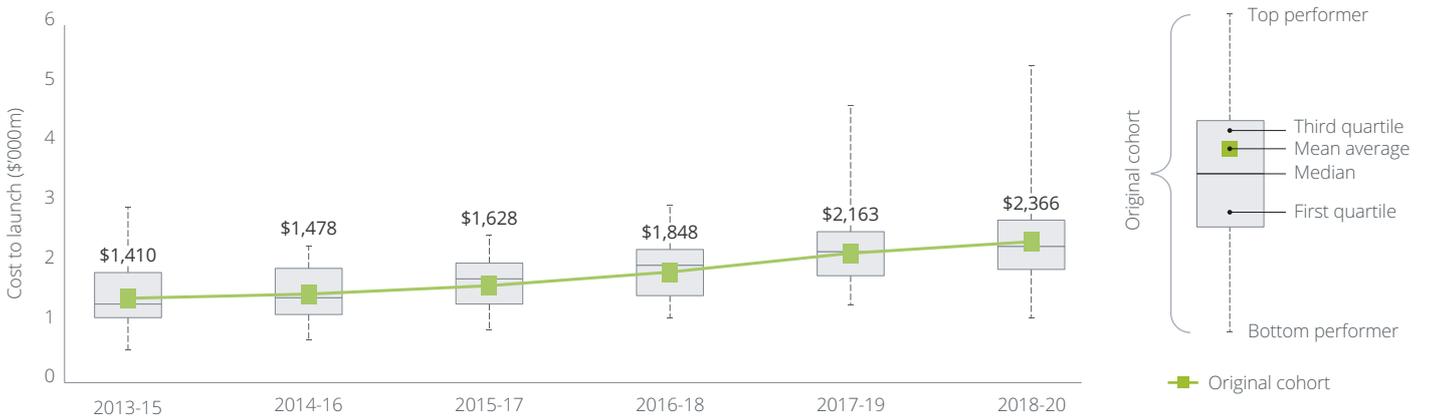
Note: 2019 numbers have been restated. For more information, see Methodology.

Source: Deloitte LLP, 2021.

Figure 24. Three-year rolling average peak sales per pipeline asset, 2013-20 – combined cohort
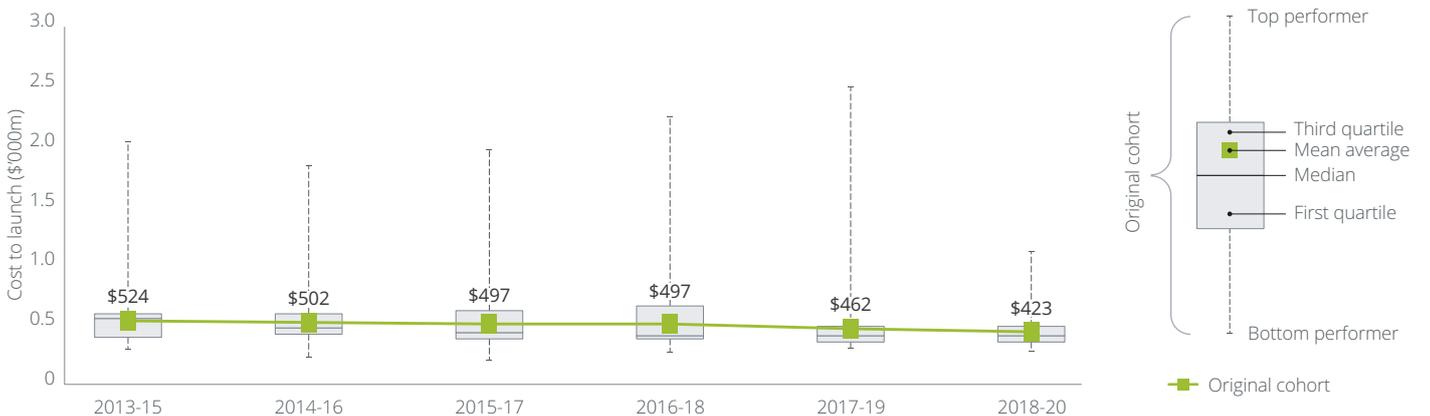
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