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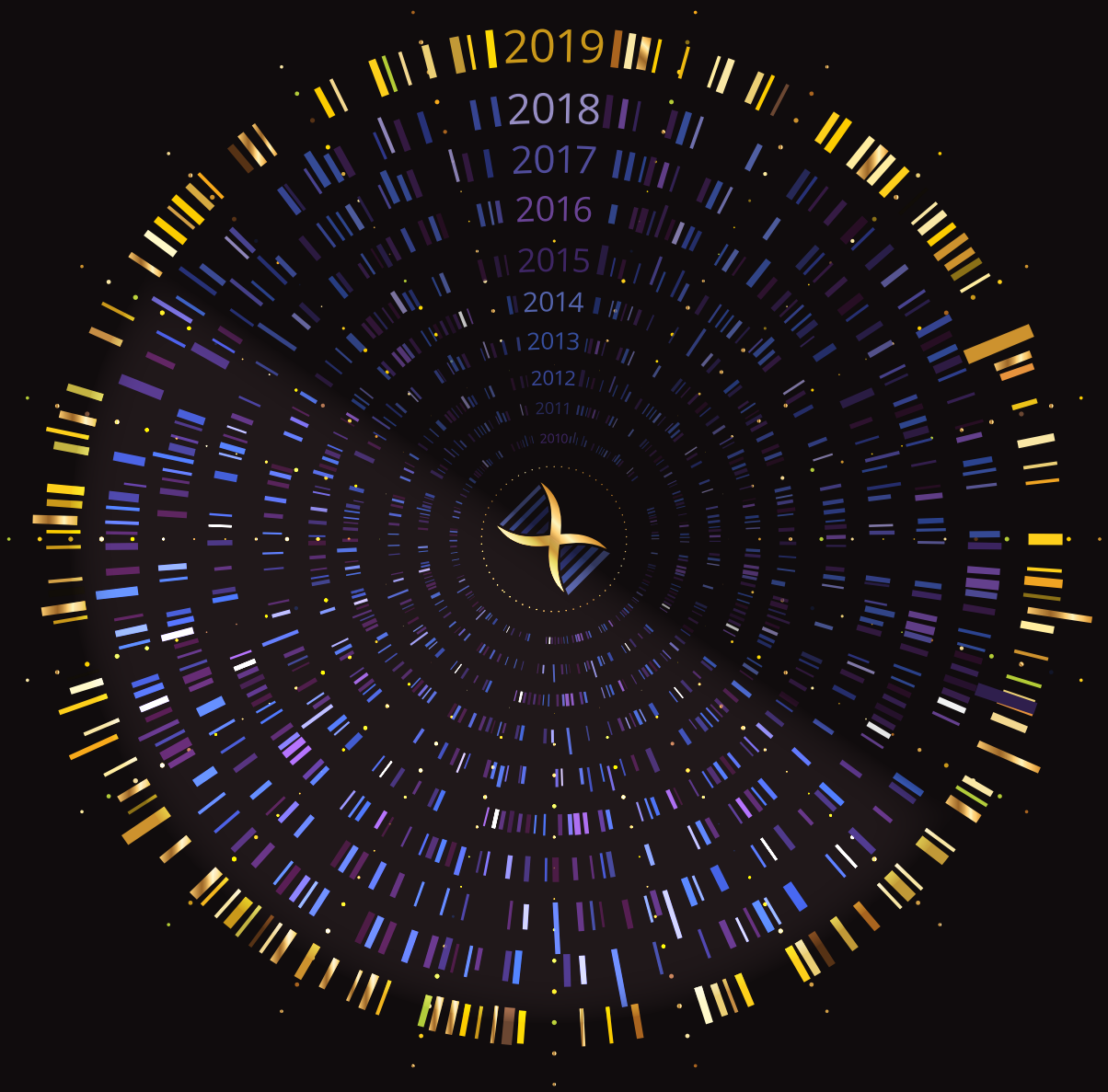

Ten years on

Measuring the return from pharmaceutical innovation 2019

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Contents

Deloitte Centre *for* Health Solutions

The Deloitte Centre for Health Solutions: Turning evidence into action
We are the research arm of Deloitte's Life Sciences and Health Care practices. The UK Centre's team of researchers, working in partnership with colleagues from the US Center for Health Solutions, aim to be a trusted source of relevant, timely and reliable insights on emerging trends, challenges and solutions. We combine creative thinking, robust research and our industry experience to develop evidence-based perspectives on some of the biggest and most challenging issues to help our clients to transform themselves and, importantly, benefit the patient.

At a pivotal and challenging time for the industry, we use our research to encourage collaboration across all stakeholders, from pharmaceuticals and medical innovation, health care management and reform, to the patient and health care consumer.

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Foreword

Welcome to *Ten years on*, the tenth annual report from the Deloitte Centre for Health Solutions exploring the performance of the biopharmaceutical industry (biopharma) and its ability to generate returns from investment in innovative new products.

Over the past ten years, our *Measuring the return from pharmaceutical innovation* series has tracked the return on investment that a cohort of 12 leading global biopharma companies might expect to achieve from their late-stage pipelines. For the past five years, we have also tracked the performance of an extension cohort of four, more specialised, biopharma companies. This has enabled us to compare and contrast performance and deepen our insight into company and pipeline characteristics that drive R&D productivity.

The analysis reveals a systemic, cross-company, decade-long decline in the productivity of R&D in our original cohort and a similar trajectory for our extension cohort. These findings reflect the R&D challenges of the industry more widely. While individual companies do experience short-term successes, the effect of rising costs and declining sales on returns seems inescapable. A decade of analysis shows that all of our cohort companies have felt the impact of these challenges. This raises critical questions for the industry, the key one being how prepared are biopharma companies to transform their R&D models? The answer will influence how companies determine their capital allocations over the next decade.

At the pipeline level, key thresholds have been crossed – more than half of pipelines are now biologics, and more than half of assets have been externally sourced. The implication remains the same – return on investment will not improve unless R&D productivity improves. The development of more targeted approaches to drug discovery and development is leading companies to adopt or optimise the use of much broader, computational technology platforms. New, data-driven R&D models will inevitably emerge. With data and information driving drug development, we envisage some biopharma companies will become data organisations, while others will transition to a leaner, more focused, science-based model with a research footprint within key innovation clusters and a growing revenue stream from specialty products and biologics.

Within this changing landscape, what has stayed constant over the decade is that companies with deep knowledge of specific therapy areas consistently earn higher returns than those who go through cycles of re-invention in new therapy areas. This is a consistent observation that challenges some of the traditional value creation narratives.

While it continues to be a challenge for leaders to unlock R&D productivity, we remain optimistic that the lessons from the last decade will help biopharma transition to a future where disease prevention and curative therapies transform care and improve the human condition. As always, we hope this report is engaging and thought provoking. We welcome feedback and look forward to discussing the implications of our findings.

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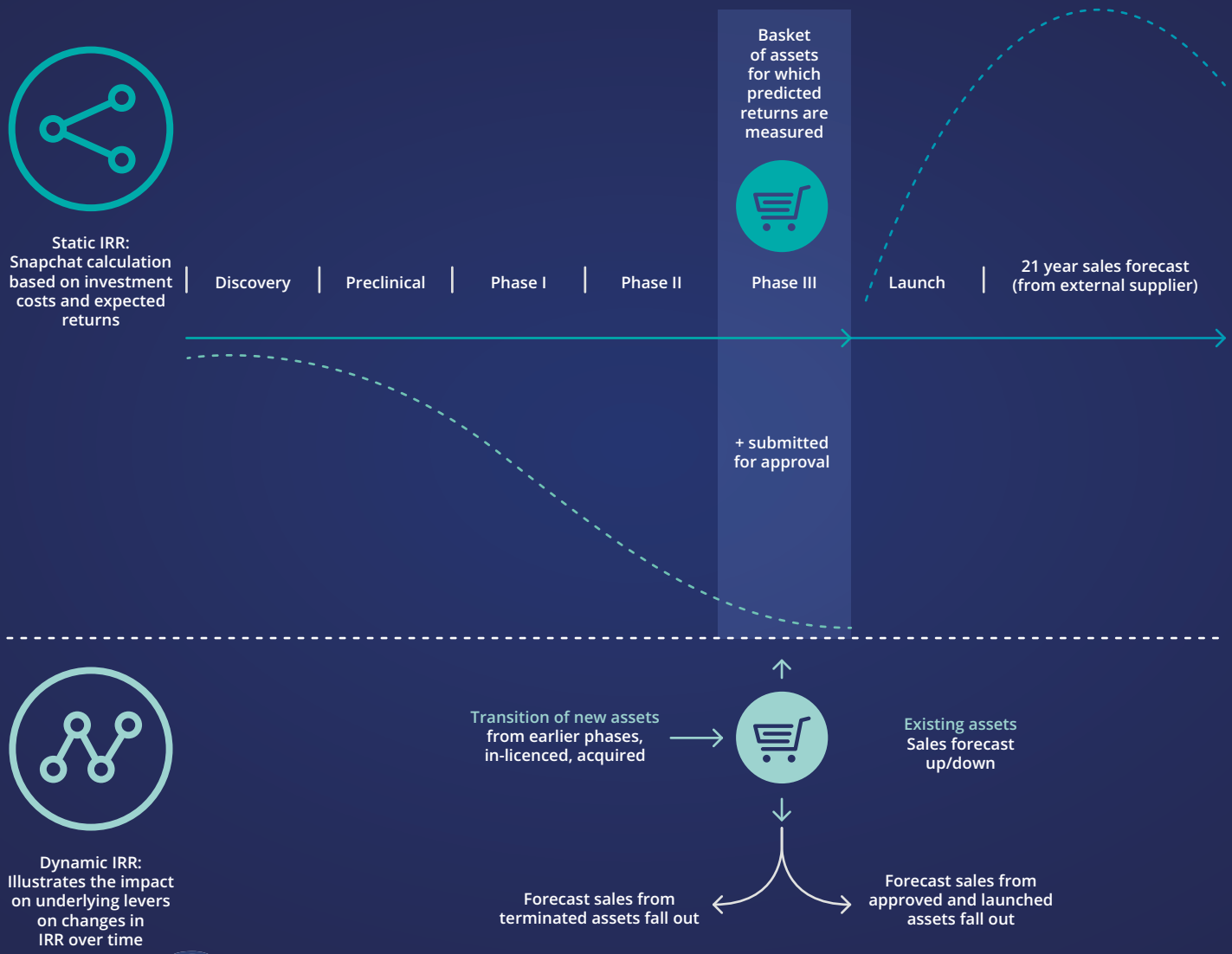
Methodology

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, more specialised companies. We use 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.

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 on the following page 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

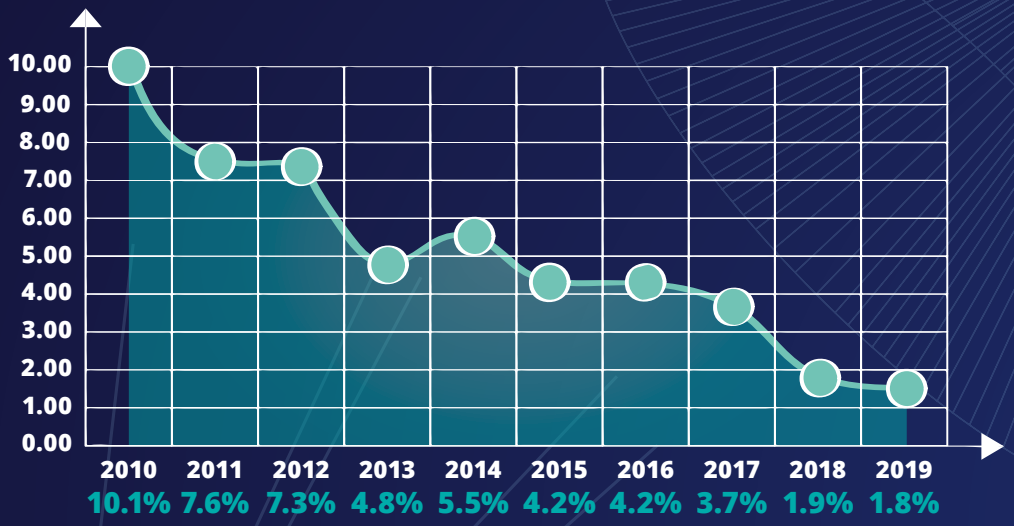


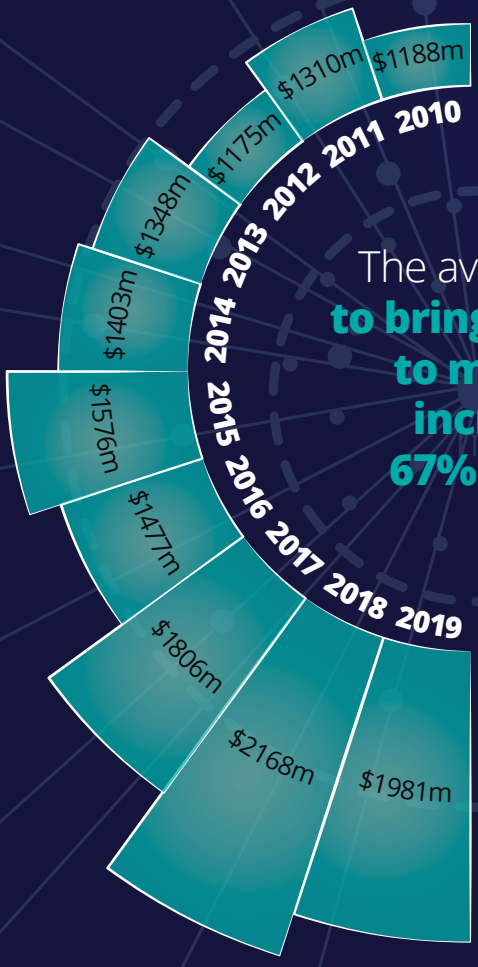
Source: Deloitte LLP, 2019

*Previously published data have been restated in this report as a result of minor corrections. While this creates minor changes in the company and consolidated figures, the trends remain consistent with the data published originally.

2019 results for large cap biopharma companies

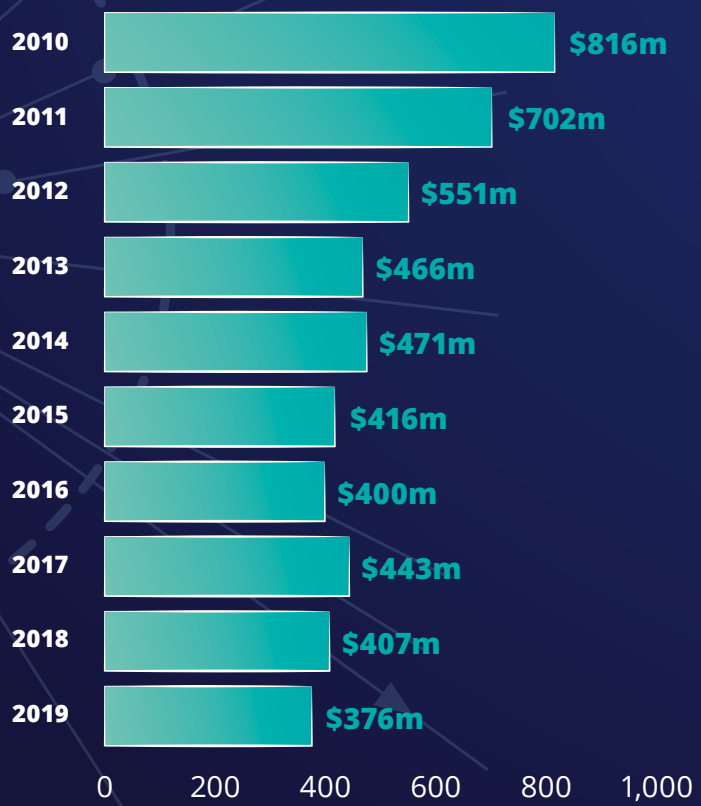
R&D returns for our **original cohort** of 12 large cap biopharma companies have **steadily declined** since 2010





The average **cost to bring an asset to market** has **increased by 67%** since 2010

Forecast peak sales per asset have **more than halved** since 2010

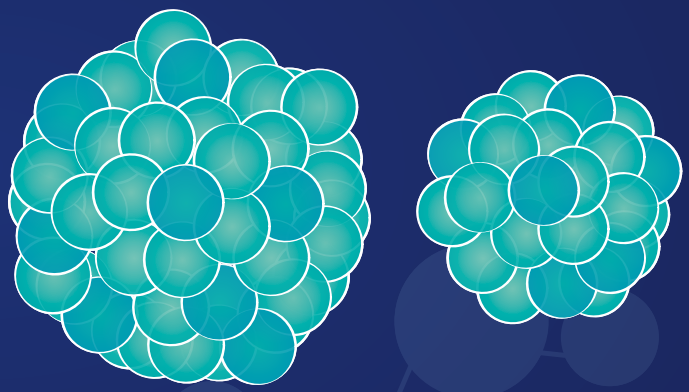


Large cap biopharma companies have **replenished** their late-stage **pipelines** in 2019

2018

2019

Our **extension cohort** of 4 more specialised biopharma companies **outperformed the original cohort** in 2019 but are facing similar **productivity challenges and declining returns**



2018 **9.3%** → **2019** **6.2%**

Forecast sales data suggest **antibody therapies are now the most valuable drug modality**, overtaking small molecules

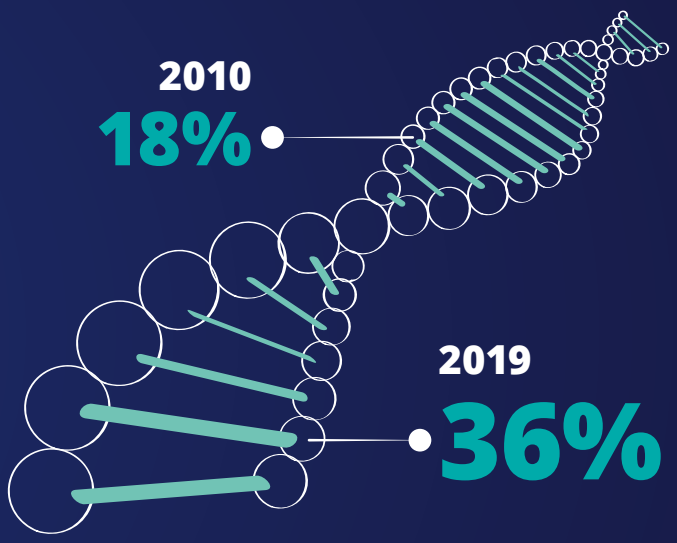
49% **small molecules**

39% **antibody therapies**

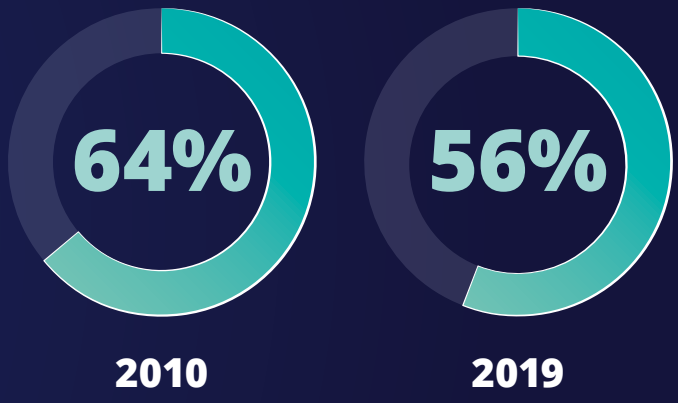
34% **small molecules**

47% **antibody therapies**

The projected value of **oncology** assets in late-stage pipelines has **doubled** since 2010



Companies in our cohorts are **sponsoring a smaller percentage of oncology trials** across the industry



Sources of innovation are changing

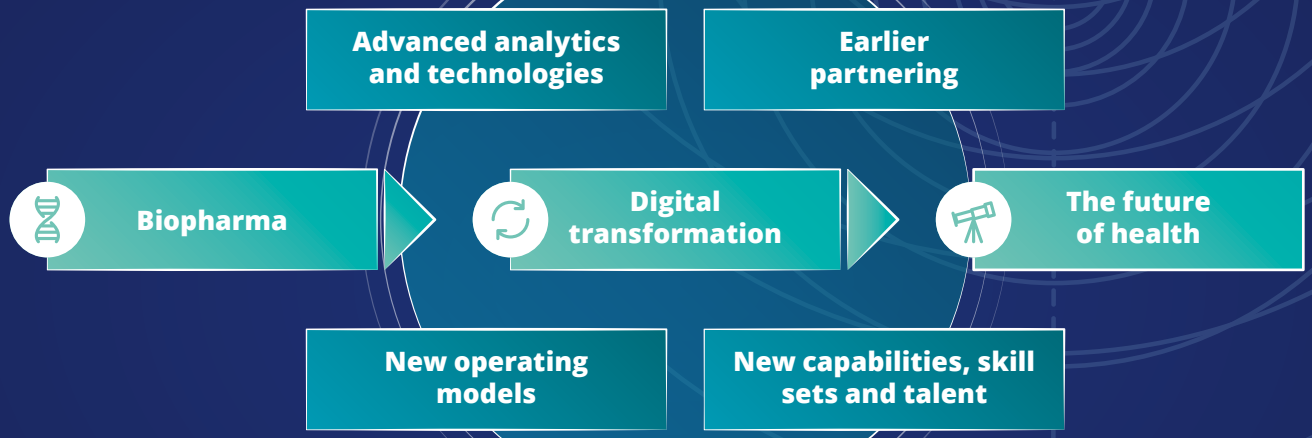
33%
acquisitions

26%
co-development

Large cap biopharma is increasingly **relying on M&A** in 2019, with **33% of forecast sales** derived from **acquisitions**

More specialised biopharma are partnering to access capability and innovation, with **26% of forecast sales from co-development**

Biopharma companies need to pursue a fundamental shift in their R&D model



The future of biopharma R&D

We continue to see a future for small molecule research, but companies that do not shift their operating models to accommodate emerging modalities risk becoming less competitive

Scientific breakthroughs will occur at an exponential pace, building on the insights derived from radically interoperable data

R&D costs will shift from traditional discovery and trial execution to a process driven by large datasets, advanced computing power and cloud storage

Advanced analytics and **technologies** will enable end-to-end automation of R&D, reducing timelines significantly

Executive summary

Decades of advances in science and technology have driven improvements in health care outcomes and influenced stakeholder expectations of the role of the biopharmaceutical industry (biopharma). However, the past decade has seen increasing pressures undermine the productivity of biopharma R&D, leading to a decade of decline in the return on investment. At the same time, innovative new treatments are changing the face of disease management. New treatment modalities and an increasing understanding of precision medicine have led to the need for new R&D models and a future where medicine is more participatory, preventative and personalised.

A decade of decline and transition

Our series *Measuring the return from pharmaceutical innovation* has provided insight into the state of biopharma R&D since 2010, analysing the return on investment that 12 large cap biopharma companies might expect to achieve from their late-stage pipelines. Each of our reports deploys a unique and consistently applied methodology for assessing the value from R&D investment. In the first four years, our analysis indicated a steady decline in average internal rate of return (IRR), along with an inverse correlation between IRR and company size. Consequently, in 2015, we introduced an extension cohort of four smaller, more specialised companies and analysed their pipelines back to 2013.
The analysis of the performance of the late-stage drug pipelines of the two cohorts provides a proxy for measuring biopharma's ability to balance R&D investment (initial and ongoing capital outlay) with the cash inflows (drug sales) the industry is projected to receive as a result of the investment. Overall, our analysis shows that both of our cohorts have seen significant declines in their expected returns over the ten years, suggesting the current high-risk, high-cost R&D model is unsustainable.

Measuring the return from pharmaceutical innovation

Our original cohort has seen their projected IRR decline from 10.1 per cent in 2010 to 1.8 per cent in 2019, down 0.1 percentage points from 2018 and 8.3 percentage points overall. However, in 2019, while eight of the 12 companies in our original cohort improved their returns compared to 2018, only one company achieved returns above five per cent, and the range in values between the top and bottom performer has narrowed to its lowest value in our series. The IRR for our extension cohort also declined to its lowest level in 2019, down from 17.1 per cent in 2015 to 9.3 per cent in 2018 to a low of 6.2 per cent in 2019, mainly due to asset terminations. However, the four extension cohort companies are still outperforming their larger original cohort peers.

Our R&D productivity measure is a factor of the cost to develop the assets in the company pipeline and the expected sales from these assets once launched. The average cost to develop an asset, including the cost of failure, has increased in six out of nine years. In 2019, our original cohort's average cost to develop an asset decreased from $2,168 million in 2018 to $1,981 million in 2019 (the cost per asset in 2010 was $1,188 million). Similarly, our extension cohort's average cost decreased from $2,805 million in 2018 to $2,422 million in 2019 (the cost in 2015 was $1,260 million).

Forecast peak sales per asset also declined for both cohorts. The original cohort's average fell below $400 million for the first time, to $376 million in 2019, down from $407 million in 2018 (the average peak sales per asset in 2010 was $816 million). For our extension cohort, forecast peak sales increased from $1,113 million in 2015 up to $1,165 million in 2018 but decreased significantly to $658 million in 2019.

Despite the fall in peak sales per asset, the average cost to develop an asset decreased for both cohorts because they successfully replenished their late-stage pipelines with assets from earlier stages of development or licensing deals. Overall, the number of late-stage pipeline assets in the original cohort's portfolio increased from 159 to 183, a three-year high and very close to the ten-year average of 186.5, while the extension cohort's portfolio increased from 23 to 30 late-stage assets.

The key drivers of the changing R&D model

Several factors are influencing R&D pipelines, including the increase in biologics in the pipeline, the length of time in development (cycle times) and sources of innovation. While the search for small molecule therapeutics defined biopharma R&D for decades, an increased focus on biologics has led to more diverse biopharma pipelines. In 2010, traditional small molecules made up 67 per cent of our original cohort's pipeline of late-stage assets, however, the proportion has fallen to 43 per cent in 2019. Antibody therapies now account for 37 per cent of the pipeline, up from 15 per cent in 2010. The proportions of other modalities, including cell and gene therapies, antisense oligonucleotides, protein-based therapies, vaccines and synthetic peptides have changed little in the past decade, despite the increased hype around recent breakthroughs. However, we expect that in future years, 'next gen' modalities will increasingly drive biopharma innovation, with biopharma companies likely to encounter numerous challenges adapting to the changes needed to develop these new modalities.

The shift in drug development towards more scientifically complex modalities and therapy areas has also affected clinical trial cycle times. This is despite efforts from regulators to introduce initiatives to accelerate drug development and approvals. Biopharma companies today are taking longer than ever to bring new drugs to market, with steady increases in average cycle time mainly due to the increasing share of the pipeline focused on oncology, which has longer average cycle times compared to other therapy areas. While biopharma companies have pursued different approaches to reduce cycle times, they have had marginal if any impact.

Moving forward, strategies will need to focus on optimising the clinical trial process and the use of digital technologies, including using artificial intelligence to expedite patient enrolment, improve protocol design and site selection, and capture patient reported outcomes and digital biomarkers.

In 2010, close to half of our original cohort's late-stage pipeline was sourced through external innovation, which historically launched at higher rates than the industry benchmark. For the past two years, over 50 per cent of both our cohorts late-stage pipelines have been sourced externally. Furthermore, an increasing proportion of new molecular entity/new active substance approvals have come from outside our cohorts. Likewise, companies from outside our cohorts are sponsoring an increasing proportion of clinical trials, rising from 44 per cent in 2010 to 57 per cent in 2019. This raises questions around the sustainability of big pharma's current innovation model, and whether smaller companies may ultimately take an increasing share of the market by developing and commercialising products independently.

Indeed, there has been an influx of private equity and venture capital investment going into the biotech market, mainly to companies focused on new modalities. Consequently, emerging companies have been able to pursue development into later stages, which in the long run will make it more difficult for big pharma to buy innovation. Big pharma will also face competition from other non-traditional competitors. In a future of health driven by shared and interoperable data, empowered consumers and scientific breakthroughs, biopharma companies will need to develop entirely different core capabilities from today.

Shaping the future of biopharma innovation

The past ten years of decline in IRR illustrates quite starkly that new models of R&D are needed. The growing number of rich datasets and advances in genomics, analytics and science more generally are providing an opportunity for every biopharma company to decide what type of R&D model will be most appropriate for their future sustainability. Data conveners, science and insight engines, and data and platform infrastructure builders will drive the future of health for biopharma.

In many ways, we maintain the 'tempered optimism' that characterised our first *Measuring the return from pharmaceutical innovation* report. We believe that biopharma companies can reverse the subsequent decade of decline that we have uncovered through our analysis to deliver a sustainable future for the industry. A lot rests on learning the lessons of the past ten years to improve R&D productivity. However, the continued challenges around rising R&D costs, declining expected peak sales, expanding regulatory requirements, more demanding reimbursement hurdles and other challenges will remain. New technologies and digital transformation offer biopharma opportunities in how they conduct R&D and engage with participants in clinical trials and with regulators. Biopharma's ability to adapt to the future of health will determine the success of the industry.

A decade of decline and transition

The past decade has brought massive changes in our knowledge of science and technology, which has driven improvements in health care outcomes and affected stakeholder expectations of the role of the biopharmaceutical industry (biopharma). While biopharma companies continue to develop increasing numbers of innovative life-enhancing and life-saving therapies, the cost of developing these therapies has continued to rise, while paying for new treatments has come under increasing scrutiny from payers, providers and patients.

At the same time, constraints around market access and pricing, changing patterns of demand and continuing downward pressure on health care budgets, have presented the industry with a volatile and highly uncertain economic environment in which to operate, let alone drive productivity improvements.

The changing prevalence of chronic diseases, including the rise of age-related diseases such as dementia and cancer, has led to many people living longer but with more complex comorbidities. Our increasing knowledge of science – particularly advances in genomics – and the fact that we know drugs do not work the same way in everyone has uncovered a growing number of areas of unmet need. As a result, the demand on existing drugs and the search for new therapies has increased, and, at the same time, attracted the attention of payers and policy maker as to the cost-effectiveness and affordability of new treatments.

The rationale for a new metric for evaluating capital allocation to R&D

Ten years ago the life sciences industry was beginning to experience a fundamental productivity challenge, as growth in investment in R&D outpaced the growth of sales without resulting in an increased output of new medicines. In the first report in our series on *Measuring the return from pharmaceutical innovation*, we hypothesised that the historical 'input-led' approach of investing 15-20 per cent of sales revenue into R&D was no longer fit for purpose. Moreover, a more effective method for assessing the value from R&D investment that took a 'whole R&D business' approach was needed.[1]

Consequently, we introduced a unique model for assessing the Internal Rate of Return (IRR) as a way of measuring the performance of the top 12 global biopharma companies by 2009 R&D spend. Each of our annual reports since then has used this consistent and objective methodology to calculate changes to the projected IRR of the late-stage pipelines of these leading biopharma companies in an attempt to determine what key drivers are impacting these changes.

Our first report showed that the top 12 biopharma companies could expect a positive return on their investment in R&D. At 10.1 per cent, the average IRR of the 12 companies was above our calculation of the group average weight adjusted cost of capital (WACC) of seven per cent, with only one company expected to generate returns that fell below this WACC. We highlighted the growing complexity of drug development compared to the 1990s and showed a steep rise in the cost of product innovation that was outpacing commercialisation success rates, resulting in companies reconfiguring how they approached drug development. However, our findings suggested a 'tempered optimism' about the future, while recognising that any adverse impacts, such as rising R&D costs, expanding regulatory requirements, more demanding reimbursement hurdles and incremental austerity-related price cuts would exert a significant downward pressure on IRR and future success.

Figure 1. Overview of past report findings, 2010-18

Year	Title	Average R&D cost ($ millions)	Average peak sales ($ millions)	IRR (%)	Key conclusions
2010	Is R&D earning its investment?	1,188	816	10.1	a 'tempered optimism' about the future, recognising that adverse impacts could decrease IRR and future success
2011	Is R&D earning its investment?	1,310	702	7.6	significant movements in IRR, biopharma need greater rigour in capital allocation decision making, more intense collaboration with peers and with payers, and to simplify the fundamentals of R&D operations
2012	Is R&D earning its investment?	1,175	551	7.3	a mixed picture of performance; companies that are successful in the business of R&D will be effective in marshalling the best science and advances in diagnostics, and in deploying a flexible, collaborative development model that focuses early on gathering evidence of value
2013	Weathering the storm?	1,348	466	4.8	significant variation in cohort performance, but cohort leaders appeared to be weathering the storm; investment in R&D remained a challenging endeavour
2014	Turning a corner?	1,403	471	5.5	slight uptick in IRR; company size appeared to inversely correlate with R&D returns, reinforcing view that smaller, more dynamic and flexible R&D units were better equipped to confront the challenges of biopharma R&D
2015	Transforming R&D returns in uncertain times	1,576	416	4.2	extension cohort introduced and were more successful; original cohort should use their scale and capability on a more focused set of TAs where they can be a market leader and gain competitive advantage
2016	Balancing the R&D equation	1,477	400	4.2	key strategic decisions around TA focus, product strategy and R&D programme design could increase pipeline value; thinking small, balancing staffing and outsourcing, lifting the burden of data complexity could reduce the cost to launch
2017	A new future for R&D?	1,806	443	3.7	improving projected returns continues to be challenging, but numerous examples of innovation demonstrate biopharma's resilience and project optimism for the future. Biopharma can increase returns if it embraces advanced technologies across the value chain
2018	Unlocking R&D productivity	2,168	407	1.9	projected returns declined to lowest level due to internal and external productivity challenges; traditional ways of working are shifting in biopharma R&D, and companies need to transform digitally and adopt new ways of working

Source: Deloitte LLP, 2019. *Previously published data have been restated in this report as a result of minor corrections. While this creates minor changes in the company and consolidated figures, the trends remain consistent with the data published originally.

A decade of analysis has yielded a wealth of insight into R&D

Since then we have published nine further reports, including this, our tenth report. Figure 1 summarises our focus and conclusions over the past nine years.
In 2014, our analysis suggested that company size appeared to inversely correlate with R&D returns. This reinforced the prevailing view at that time that smaller, more dynamic and flexible R&D units were better equipped to confront the challenges of biopharma R&D. To test this hypothesis, we introduced an extension cohort in 2015, comprising four mid-to-large cap, more specialised companies and analysed their pipelines dating back to 2013 to gather insights about the extension cohort's approach and the value of therapy area (TA) focus. We found that by concentrating R&D efforts in areas of significant unmet need, the extension cohort had an average IRR of 17.1 per cent (outperforming by far the original cohort's returns of 4.2 per cent).

We therefore suggested that companies in our original cohort should consider using their scale and capability on a more focused set of TAs where they can be a market leader and gain competitive advantage. Moreover, that future winners in R&D would be companies that exhibit an end-to-end understanding of disease areas, patient behaviours, and improve their targeting and delivery mechanisms.

In recent reports, our analysis has shown that, despite launches of many successful products, the long-term outlook for the industry is increasingly challenging. While the extension cohort has consistently outperformed the original cohort, it has also seen significant declines in its returns, and the challenges that once only plagued our original cohort companies are now systemic across the industry. More specifically, new drugs are becoming much more expensive to develop and are targeting much smaller patient populations. Biopharma companies therefore need to reduce the costs of their R&D or increase the value of their late-stage pipeline assets to improve productivity.

"In recent reports, our analysis has shown that, despite launches of many successful products, the long-term outlook for the industry is increasingly challenging."

In the future, biopharma's approach to R&D will need to adapt

As health care increasingly moves from treatment to prevention and even cure, building robust evidence to back health care claims, as well as improving relationships with patients based on trust, is essential to obtaining both regulatory approval and patient engagement.

In addition, the past ten years have seen a growing number of 'new entrants' competing with big pharma for patients and patients' data, including developing new approaches to treatment. Big tech companies, as well as innovative start-ups, are using complex digital tools and algorithms to try and help patients stay healthy and manage their conditions more effectively. Meanwhile, biopharma companies are beginning to embrace a truly patient-centric approach, establishing alternative approaches to disease management and a more proactive approach to regulation.

The latter part of this decade has continued to be increasingly challenging but also very innovative. The rest of this report provides the results of our 2019 analysis of the return on investment on R&D and evaluates some of the key drivers that could help deliver a sustainable future for biopharma R&D.

Measuring the return from pharmaceutical innovation

Analysis from the first nine years of our *Measuring the return from pharmaceutical innovation* series concluded that a transformational change in R&D productivity is required to reverse declining trends in R&D returns across the biopharma industry. Analysis from this, our tenth report, shows that this conclusion is still true today.

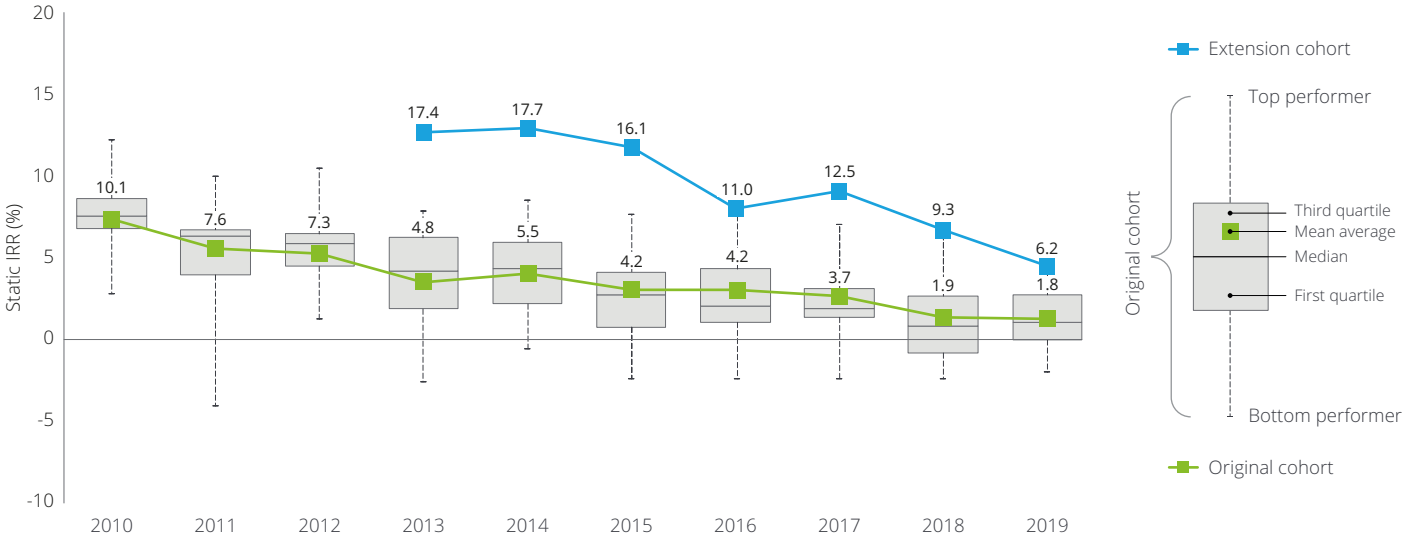
The original cohort's projected returns have declined slightly to 1.8 per cent

In 2019, the consolidated average IRR for the original cohort has declined to 1.8 per cent – a slight decrease of 0.1 per cent from 2018, but a decrease of 8.3 per cent from 2010 (Figure 2). This represents an average decline of 0.83 per cent per year.

The wide variations in performance between individual companies in the original cohort that have been a feature of previous analyses are no longer evident, as the range in values from the top and bottom performer has declined from 10.4 per cent in 2018 (top performer: 7.5 per cent, bottom performer: -2.9 per cent) to 7.1 per cent in 2019 (top performer: 5.1 per cent, bottom performer: -2.0 per cent). In addition, while eight of the 12 biopharma companies in our original cohort improved slightly from 2018, only one company achieved returns above five per cent. On a three-year rolling average basis, the average IRR of the original cohort is now tracking at 2.5 per cent for 2017-19 (Figure 26 in Appendix). Please see the section dedicated to the extension cohort beginning on page 18 for an analysis of their performance.

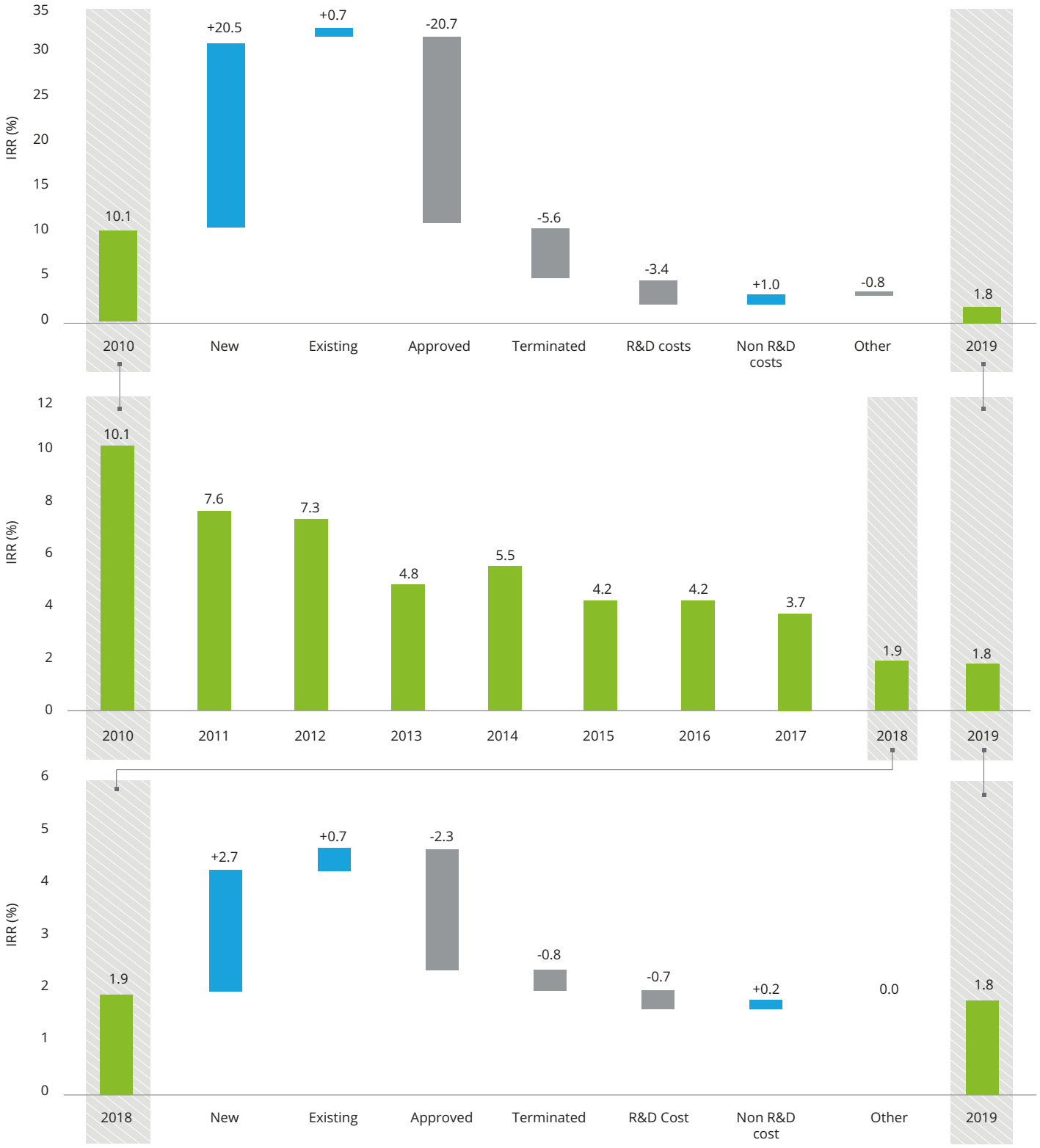
Figure 3 shows the aggregate drivers of change for the original cohort between 2010 and 2019, our calculation of the year-on-year IRR and illustrates the key drivers of change between 2018 and 2019. Year-on-year drivers of change in IRR for the original cohort over the past decade (2010-19) are shown in Figure 27 in the Appendix.

Figure 2. Return on late-stage pipeline, 2010-19 – original and extension cohorts



Source: Deloitte LLP, 2019

Figure 3. Drivers of change in IRR 2010-19 consolidated, 2010-19 year-on-year and 2018-19 – original cohort



Source: Deloitte LLP, 2019

Due to rounding, numbers presented throughout this document may not add up precisely to the totals provided, and percentages may not precisely reflect the absolute figures.

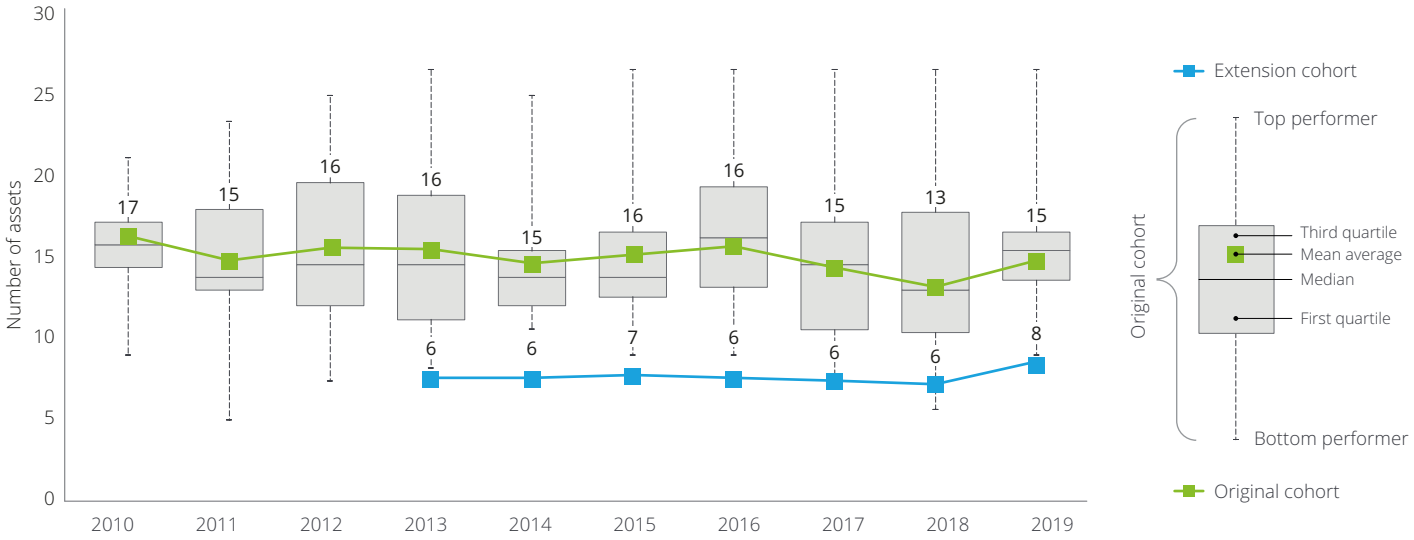
Between 1 May 2018 and 30 April 2019, the original cohort launched a total of 36 approved assets, with forecast total sales of $152 billion. This represented a 2.3 percentage point decline in projected returns, the fourth highest decrease due to approvals since our analysis began in 2010.

Set against successful approvals, late-stage R&D continues to be inherently risky, which is underlined by the decrease in IRR due to late-stage failures. In 2017 and 2018, assets removed from the pipeline due to terminations contributed to a 0.7 percentage point decline in IRR. This year, terminations have contributed to a 0.8 percentage point decline in IRR. While this is not noticeably different from previous years, the overall effect of terminations has been responsible for a decline of 5.6 percentage points since 2010.

A consistent trend highlighted throughout our *Measuring the return from pharmaceutical* innovation series has been that, while companies continue to innovate, they have been unable to replenish late-stage pipelines at a rate that compensates for the successful approval and flow of value into the commercial pipeline and loss through late-stage attrition. This year has seen an increase of 2.7 percentage points due to 60 new assets entering the pipeline, which is 1.1 percentage points higher than in 2018. These assets have forecast lifetime sales of $332 billion.

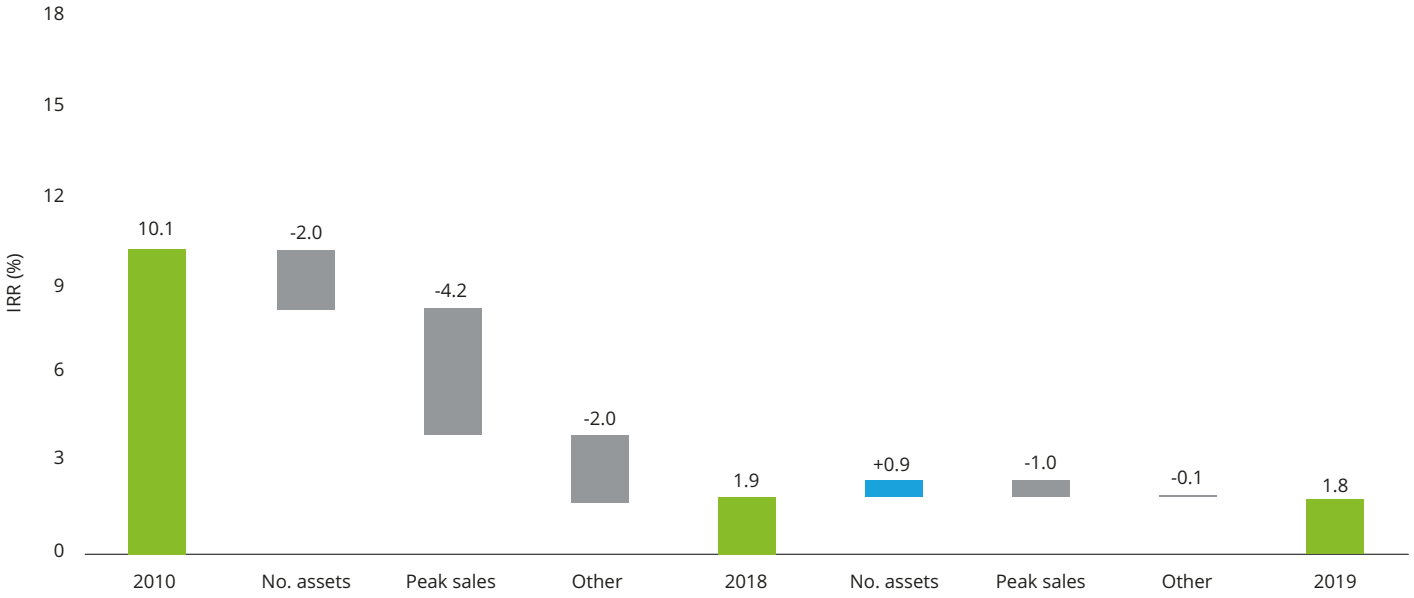
Similar to 2018, and for the fourth time in our series, the original cohort has been successful in de-risking and increasing the value of projected returns from existing late-stage pipeline assets, with a 0.7 percentage point increase in 2019. This increase in forecast revenues from existing assets has been largely driven by positive clinical trial data, class effect and delays to loss of exclusivity in forecasting assumptions.

Figure 4. Average number of late-stage pipeline assets, 2010-19 – original and extension cohorts



Source: Deloitte LLP, 2019

Figure 5. Overall impact of pipeline factors on change in IRR, 2010-18 and 2018-19 – original cohort



Source: Deloitte LLP, 2019

Due to rounding, numbers presented throughout this document may not add up precisely to the totals provided, and percentages may not precisely reflect the absolute figures.

Declining returns are the result of internal and external productivity challenges

In recent years, we have seen declines in the number of assets in the original cohort's late-stage pipeline, which reached a low of 159 in 2018, an average of 13.25 per company. However, there is significant variation between the companies (from four to 21) (Figure 4). This year the number of late-stage assets has increased to 183, a three year high and very close to the ten year average of 186.5, corresponding to an average of 15.25 assets per company, with the range narrowing from eight to 22. The increase in the number of assets in late-stage development has contributed to a 0.9 percentage point increase in IRR between 2018 and 2019 (Figure 5).

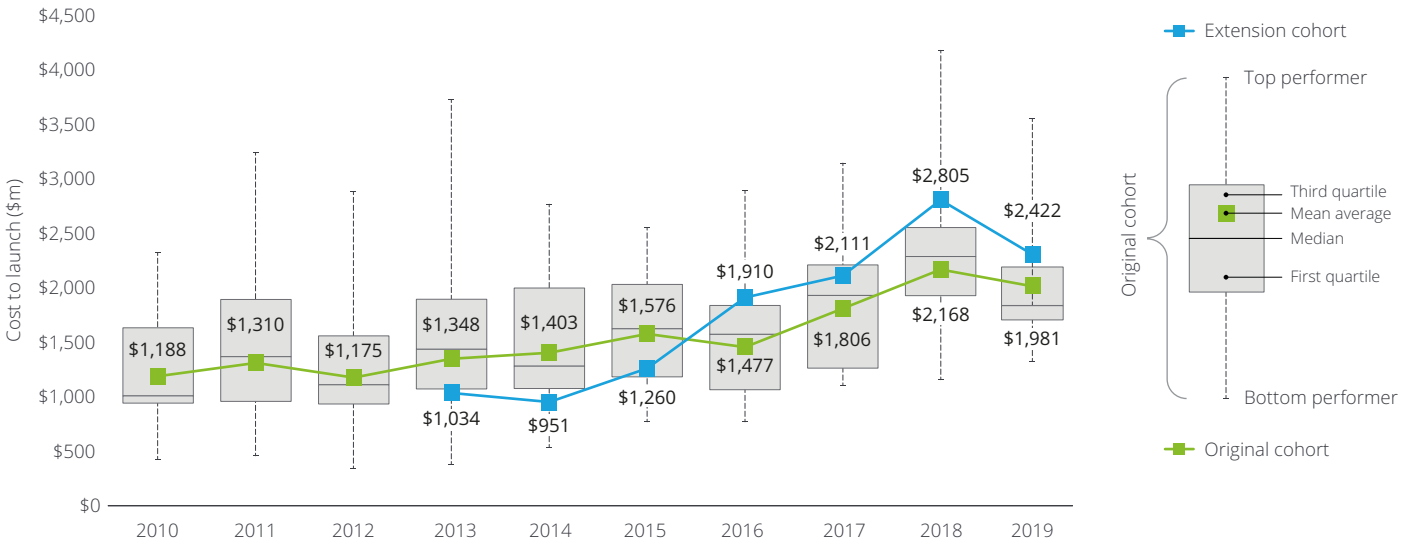
The average cost to develop an asset has decreased due to pipeline replenishment

Our cohort companies spent $79 billion on R&D in 2019, corresponding to an increase of 17 per cent in underlying R&D expenditure since 2010. However, due to the increase in the number of pipeline assets, the average cost to develop an asset in 2019 is $1,981 million, a decrease of $187 million from 2018 (Figure 6). At constant late-stage asset numbers (159 from 2018), the average cost per asset would have increased to $2,280 million, an increase of $112 million.

On a three-year rolling average basis, the average R&D cost is now tracking at $1,971 million for 2017-19 (Figure 28 in Appendix).

With the decline in average cost to develop an asset, we also see a decline in the range from the top and bottom performers from our cohort, although this variance is still significant across our cohort companies.

Figure 6. Average R&D cost to develop a compound from discovery to launch, 2010-19 – original and extension cohorts



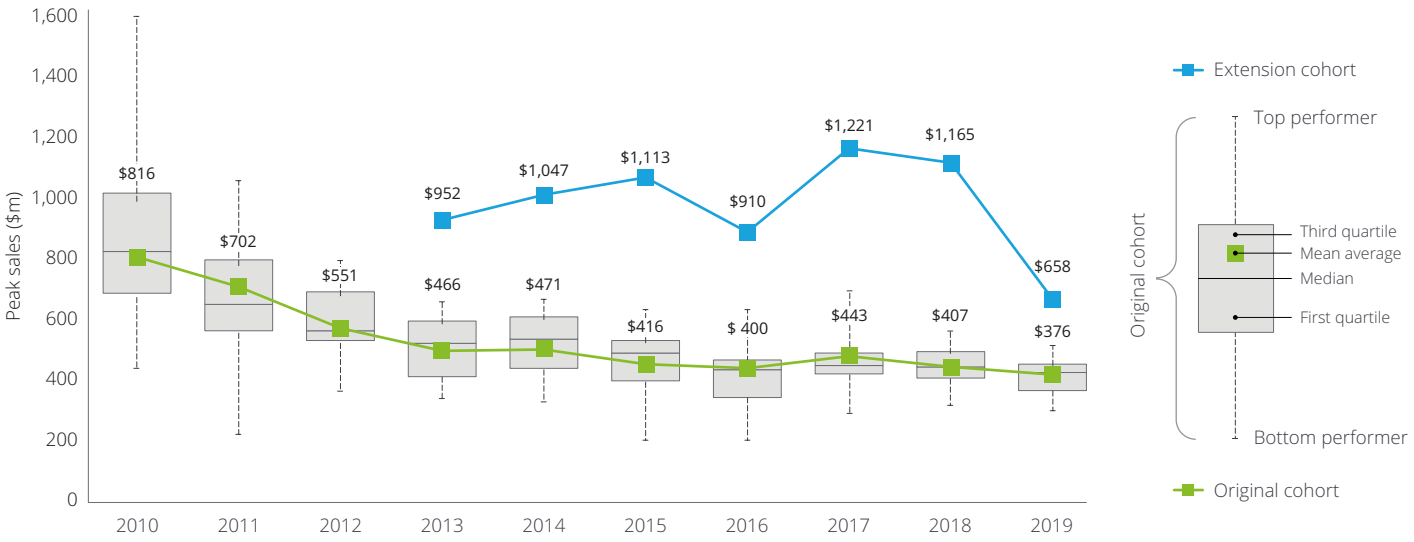
Source: Deloitte LLP, 2019

Forecast peak sales decline slightly in 2019

The decrease in the average forecast peak sales per asset has, and continues to be, the greatest reason for the decline in IRR of the pipeline factors highlighted in Figure 5. This year has seen a decline in average forecast peak sales per pipeline asset from $407 million in 2018 to $376 million in 2019 (Figure 7). The range in average forecast peak sales this year is the lowest is has been over the last ten years. On a three-year rolling average basis, average forecast peak sales per asset is now tracking at $408 million for 2017-19 (Figure 29 in Appendix).

"The decrease in the average forecast peak sales per asset has, and continues to be, the greatest reason for the decline in IRR."

Figure 7. Average forecast peak sales per pipeline asset, 2010-19 – original and extension cohorts



Source: Deloitte LLP, 2019

The extension cohort is starting to face productivity challenges similar to the original cohort

The extension cohort has seen a much more dramatic decline in IRR than the original cohort in 2019. However, the four extension cohort companies are still outperforming their larger original cohort peers, with an IRR of 6.2 per cent, a value not bettered by the original cohort since 2012 (Figure 2).

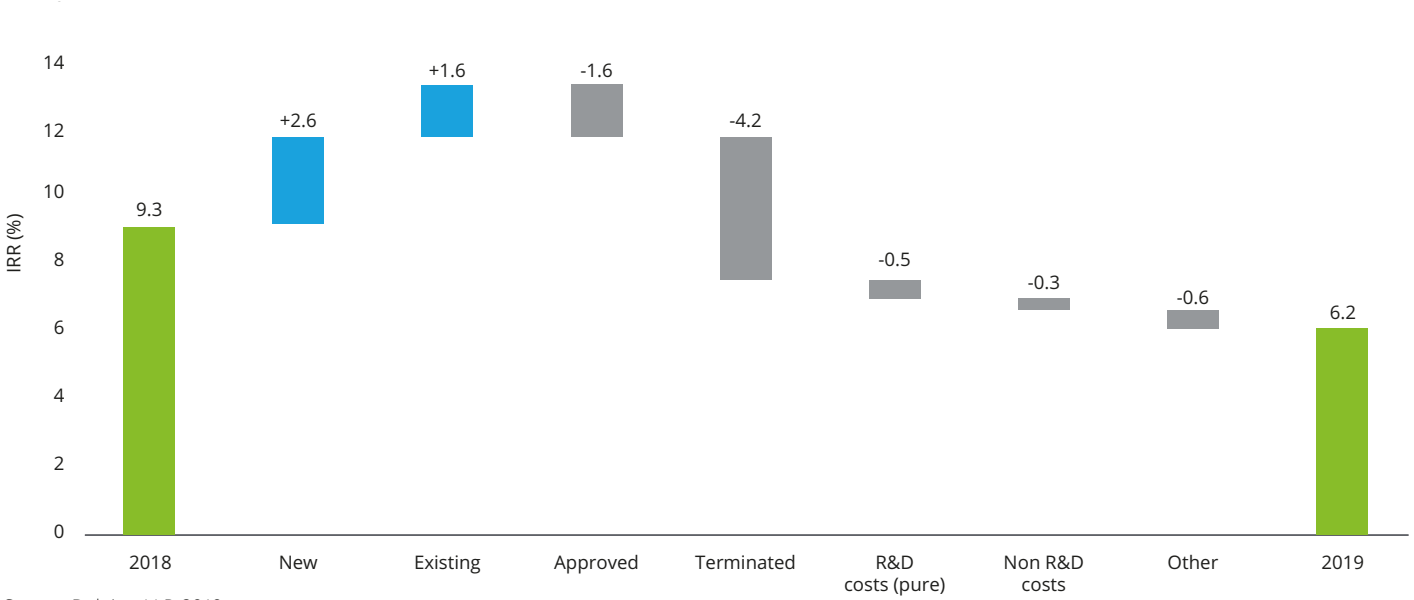
In our 2018 analysis, the extension cohort saw an increase in its average cost to bring an asset to market rise to $2,805 million. In 2019, this cost remained above $2 billion for the third year running but declined to $2,422 million (Figure 6). The primary reason for this decline for the extension cohort is due to the increase in asset numbers across the cohort, which increased from an average of six per company in 2018 to eight per company in 2019 (Figure 4), reversing a trend we have seen over recent years.

Average forecast peak sales for the extension cohort fell dramatically below $1 billion for the first time since 2016, to $658 million from $1,165 million in 2018 (Figure 7). This is the third time that the extension cohort has failed to achieve average forecast peak sales of blockbuster status ($1 billion or more) in our analysis, but this stark contrast to recent years is mainly due to one forecast high-value asset failing to gain regulatory approval, and at the cut-off point of our analysis was considered terminated.

Our 2018 analysis saw a 0.8 percentage point improvement in IRR due to existing assets that remained in the pipeline year-on-year.[2] The primary driver of this increase was positive trial data, and to a lesser extent, class effect and competitor failure. In 2019 we have seen a similar trend, resulting in a 1.6 percentage point increase in IRR due to existing assets (Figure 8). However, IRR declined in 2019 due to terminated assets of 4.2 percentage points, corresponding to three assets, which is the largest decline due to terminations recorded.

"The extension cohort has seen a much more dramatic decline in IRR than the original cohort in 2019."

Figure 8. Drivers of change in IRR, 2018-19 – extension cohort



Source: Deloitte LLP, 2019

Due to rounding, numbers presented throughout this document may not add up precisely to the totals provided, and percentages may not precisely reflect the absolute figures.

"Average forecast peak sales for the extension cohort fell dramatically below $1 billion for the first time since 2016, to $658 million from $1,165 million in 2018."

The key drivers of the changing R&D model

Biopharma's future will be focused on developing therapies for the multiple diseases that still lack treatments and creating more precise treatment regimens that target smaller populations or individual patients. Developing these treatments brings new challenges. Biologics that target smaller groups of patients are more expensive and time-consuming to develop, and inherently generate less revenue. To improve R&D productivity, there is also a need to shorten clinical cycle times and develop better understanding of the impact of different sources of innovation and the implications of capital markets.

The growing importance of biologics

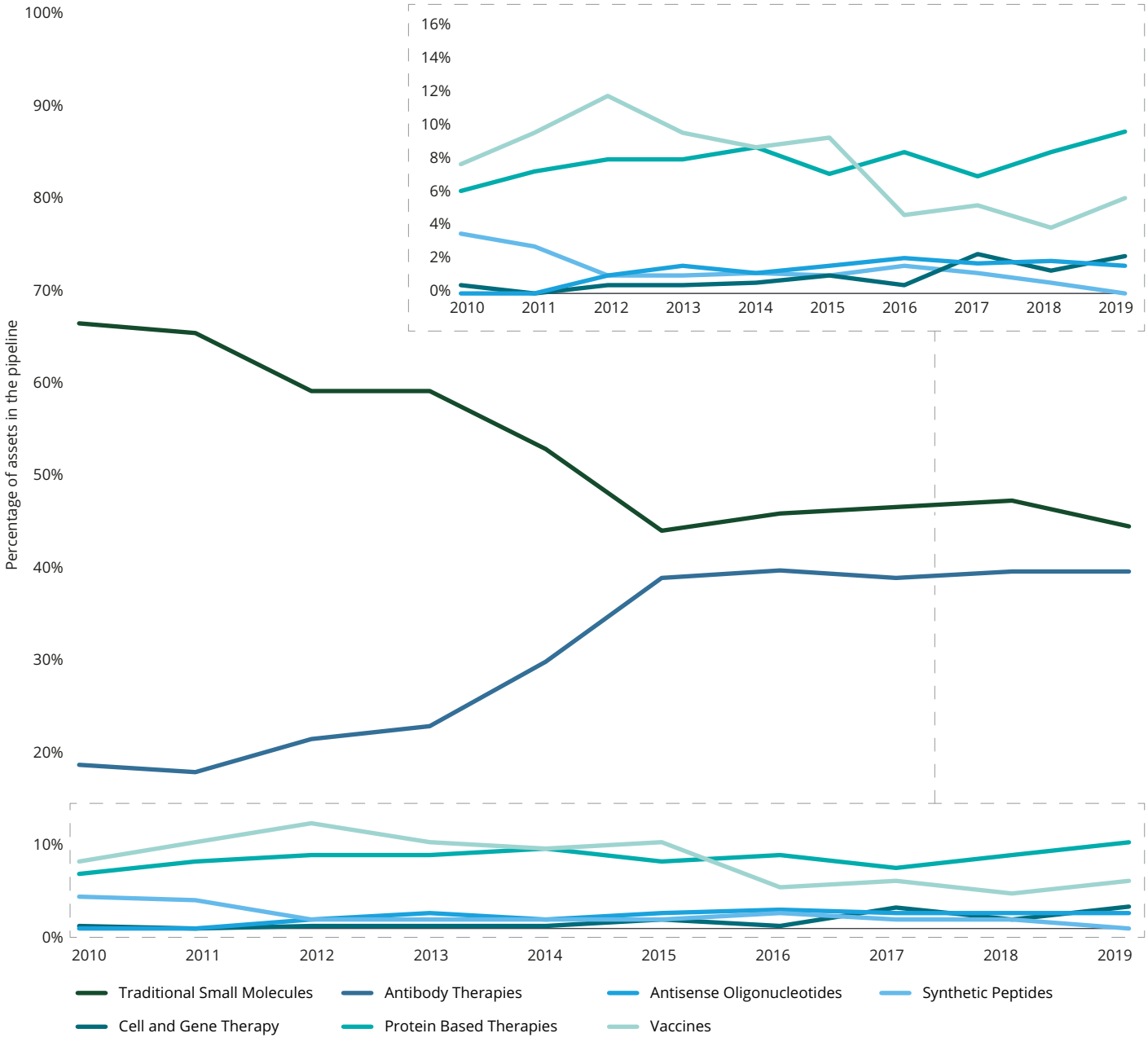
Until the 1990s, with the exception of vaccines, drug development focused almost entirely on chemically synthesised small molecule therapeutics, which still make up 90 per cent of drugs on the market today.[3] These products tend to target large populations of patients in a 'one-size-fits-all' approach and earned significant sales revenue. In 2010, biopharma companies came under increasing pressure to compensate for the significant loss of patent protection around many of their products, particularly small molecule products, due to competition from generics.[4,5] Deloitte's 2010 report, *The future of the life sciences industries: Aftermath of the global recession,* estimated that the biopharma industry could lose as much as $60 billion in revenue due to drugs going off patent in 2010 and 2011.[6] By 2018, generics made up more than 80 per cent of the volume of drugs dispersed around the world, and by 2022 are expected to make up almost 30 per cent of total drug sales worldwide.[7]

While small molecules are still a vital aspect of most biopharma companies' late-stage pipelines, the competition from generics – alongside advances in science and technologies – have driven biopharma companies to seek other drug modalities including innovative new biologically based treatments (biologics). This has changed the overall composition of the pipeline. However, while biologics have higher specificity and can be more effective, they target smaller populations, are more expensive to produce and, consequently, cost more. They are therefore prescribed much less than small molecules. In 2017, in the US, biologics accounted for only two per cent of all prescriptions, but accounted for 37 per cent of net drug spending.[8]

Only six of the 21 drugs approved by the US Food and Drug Administration (FDA) in 2010 were biologics. Similarly, of the 29 drugs approved by the FDA in 2011, only six were biologics. Overall, between 2010 and 2017, the FDA approved 63 biologics compared to 199 small molecules.[9] In 2018, however, 17 of the 59 new drugs approved by the FDA were biologics, and through 31st October 2019, eight of the 33 drugs approved so far have been biologics.[10]

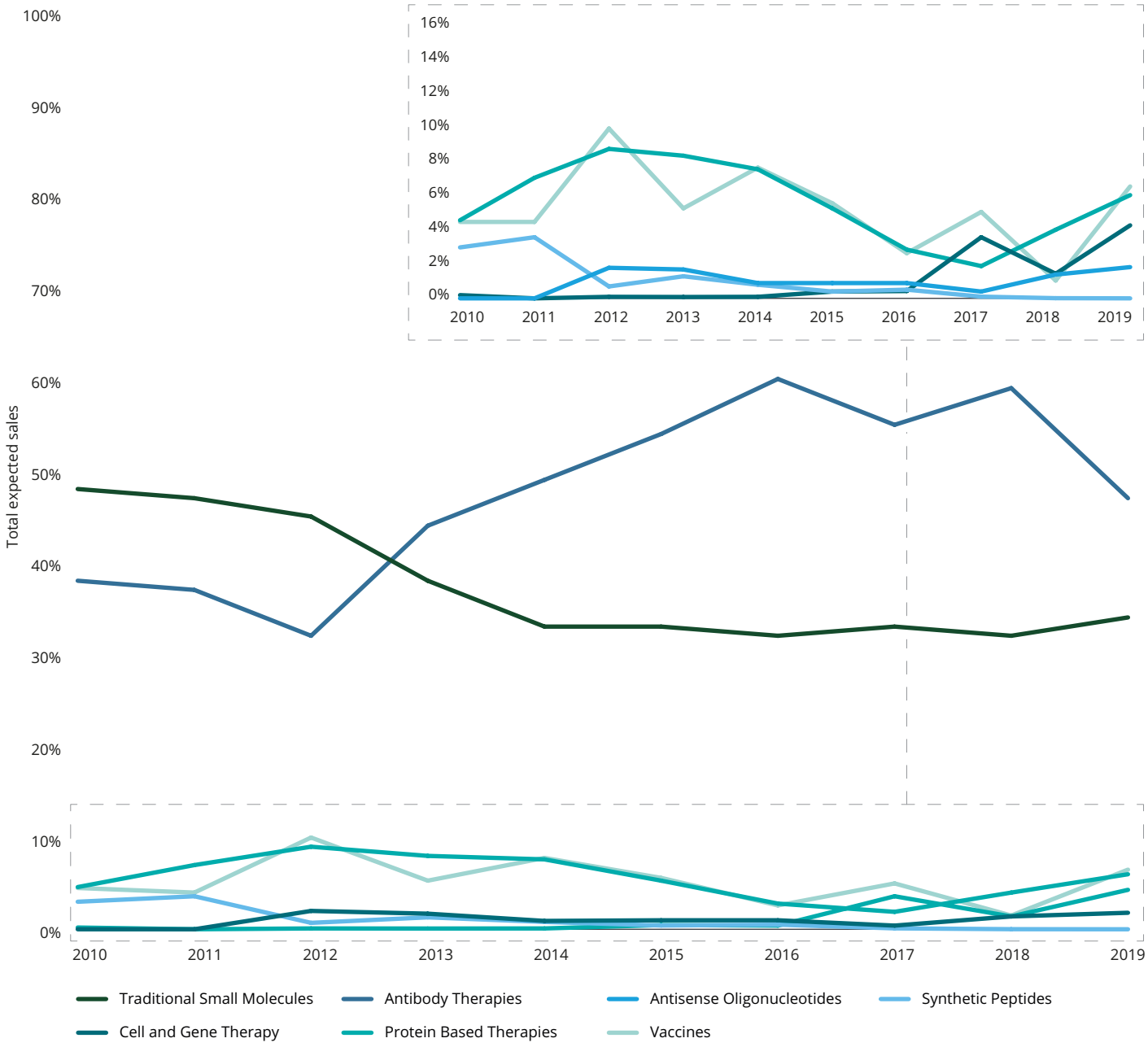
In our 2010 analysis, 67 per cent of the assets in our original cohort's pipeline were traditional small molecules; in our 2019 analysis, the proportion of small molecules had fallen to 43 per cent (Figure 9). Antibody therapies, which made up 15 per cent of the assets in our cohort's pipeline in 2010, now account for 37 per cent of the pipeline. Interestingly, there has been little change in the overall percentage of other modalities in the pipeline in the past decade, including cell and gene therapies, antisense oligonucleotides, protein based therapies, vaccines and synthetic peptides (Figure 9).

Figure 9. Pipeline focus by modality, 2010-19 – original cohort



Source: Deloitte LLP, 2019

Figure 10. Percentage of total forecast sales per modality by year, 2010-19 – original cohort



Source: Deloitte LLP, 2019

In addition to the changing ratio of small molecules to biologics, another notable point is the percentage of total forecast sales per modality by year (Figure 10). In 2010, small molecules made up 49 per cent of the total proportion of forecast sales, while in 2019 this percentage has dropped to 34 per cent. Antibody therapies made up 39 per cent of total forecast sales in 2010, jumping to 47 per cent in 2019.

Today, biopharma is facing a biologics patent cliff, leading to the emergence of biosimilars, which is expected to put $251 billion in sales of biologics at risk between 2018 and 2024.[11] Biosimilars take much longer than generics to develop, as they still have a relatively challenging regulatory pathway and are therefore still expensive to develop and buy.[12] Nevertheless, in 2018 biosimilars were making notable inroads.[13] Market forecasts suggest the biosimilar market will to grow at 32 per cent compound annual growth rate (CAGR) from 2018-23, with 42 per cent of the growth coming from Europe.[14]

Deloitte's view

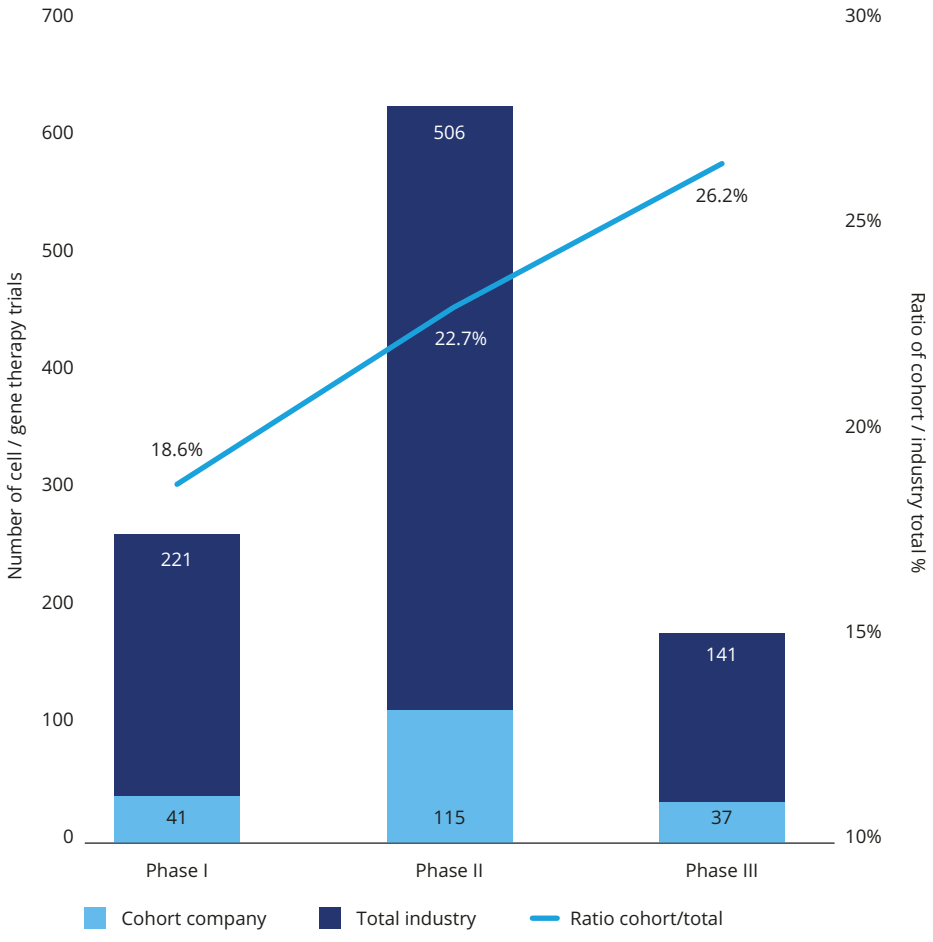
The changing proportion of modalities in biopharma pipelines reflects our increasing knowledge of science and the drive to develop treatments for diseases for which there is no treatment. Small molecules still make up the majority of our original cohort's pipeline, but antibody therapies are now expected to deliver the most revenue. While the increasing availability of biosimilars is a more cost-effective way of developing new assets and improving patient access to innovative medicines, their introduction increases competition and puts significant biopharma revenue at risk, albeit at a premium to small molecule generic versions. Biopharma companies will need to innovate to replace this lost revenue with new products, specifically by developing new, more cost-effective approaches to biopharma R&D.

'Next gen' modalities will increasingly drive innovation in biopharma

The progression of the drug development paradigm to include biologics has had a significant impact on the biopharma business model. While small molecules can be produced easily in large, uniform quantities through a well-defined process, production of biologics is much more complicated and yields a much smaller quantity of active drug. Scaling up the production of biologics is also more difficult, as maintaining purity and reducing batch-to-batch variability is challenging.[15]

'Next gen' therapies take these differences a step further, and although biopharma companies are increasingly focusing on these modalities, particularly cell and gene therapies, they face numerous challenges adapting to the development and manufacturing of these products (Figure 11). In the same way that biologics generally target smaller populations, 'next gen' therapies often target individual patients – sometimes as single treatments – resulting in truly personalised medicine. Recently, *ex vivo* (where cells are genetically modified outside the body) cell and gene therapies have generated considerable excitement on their potential to cure previously incurable diseases. However, these therapies have also been subject to increasing regulatory and health technology assessment scrutiny, including significant controversy over affordability.

Figure 11. Proportion of cell and gene therapy Phase I-III trials sponsored by companies within our cohorts vs industry total



Source: Deloitte LLP, 2019

Nevertheless, *ex vivo* cell and gene therapy sales are forecast to reach $3 billion in 2022, spurred by as many as 200 investigational new drug applications each year by 2020, and 15 to 20 approvals each year by 2025. The largest share of this market currently comes from chimeric antigen receptor T cell (CAR-T) therapies (Case study 1). Similarly, gene therapies (Case study 2) and antisense oligonucleotides (Case study 3) are also poised to impact the biopharma industry. These therapies are good exemplars of the challenges biopharma companies face with 'next gen' therapies.

Mitigating strategies include improving:

- **patient access:** 'next gen' therapies are highly customised, clinically intensive and costly. Biopharma companies would benefit from identifying the combination of factors that lead to successful treatment through informatics, engaging early and often with regulators, demonstrating the treatment's value to patients and offering pricing consistent with that value[17]
- **supply chain and manufacturing:** cell and gene therapies require a specialised, patient-centric, clinically connected value chain and distribution model prior to commercialisation. Non-traditional partners and sources of talent may be able to help bridge capability gaps[18]
- **customer and patient engagement:** engagement is critical for success with cell and gene therapies. Biopharma companies should offer patients access to treatment and logistics support through a technology-enabled multi-channel model, and ensure clinicians in specialist treatment centres receive appropriate training and ongoing certification[19]
- **health care provider (HCP) networks:** growing a network of HCPs and selecting treatment sites are critical for cell and gene therapies. Biopharma companies should consider clinical and business factors when choosing treatment centres, develop partnerships with centre personnel to understand workflow issues and areas of desired support, and align treatment protocols across manufacturers.[20]

Case study 1
CAR-T therapies use a patient's own immune cells to fight tumours

In CAR-T therapies, T cells are isolated from a patient and genetically modified to target cancer cells. After a period of growth and expansion, the modified T cells are infused back into the patient, where they target and kill cancer cells. Response rates have been as high as 70-90 per cent, and some patients have experienced greater than one-year remissions.[21] However, these treatments are high-risk, and adverse reactions can be life threatening, requiring specialised treatment centres with specially trained clinical staff.

The first two CAR-T therapies were approved by the FDA in 2017:

- **Kymriah® (tisagenlecleucel)** – for paediatric acute lymphoblastic leukaemia (ALL). The European Commission granted marketing authorisation to Kymriah® in August 2018, and the National Institute for Health and Care Excellence (NICE) recommended its addition to NHS England's Cancer Drugs Fund in September 2018. In January 2019, NICE recommended Kymriah® for adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).
- **Yescarta® (axicabtagene ciloleucel)** – for advanced lymphoma in adults. The European Commission granted marketing authorisation to Yescarta® in August 2018, and the NICE recommended its addition to NHS England's Cancer Drugs Fund in October 2018.

Although to date the FDA has approved only two CAR-T therapies, a third CAR-T therapy for lymphoma, lisocabtagene maraleucel, is currently in Phase III clinical trials and, if approved, the combined revenue from all three CAR-T therapies is predicted to reach $2.4 billion in 2027.[22] Furthermore, there are now over 600 clinical trials involving CAR-T therapies.[23]

Case study 2
Gene therapy breakthroughs

Gene therapy involves the introduction of genetic material into specific patients to treat underlying genetic causes of disease. Despite a lengthy and convoluted journey from research to clinical application, recent advances in gene editing technologies and the development of delivery vectors are now allowing gene therapies to bring new hope to patients.

In December 2017, the FDA approved Luxturna® (voretigene neparvovec), a gene therapy drug for the treatment of biallelic RPE65 mutation-associated retinal dystrophy. The RPE65 gene encodes an enzyme that is involved in the biochemical reactions that occur during light capture in the retina. Inherited mutations to RPE65 are rare, but they can lead to progressive vision loss and eventual blindness, usually by the time patients are young adults. Luxturna® was the first directly administered, adeno-associated virus vector-based gene therapy approved by the FDA that targets a disease caused by mutations in a specific gene. It was approved by the European Medicines Agency (EMA) in September 2018 and, a year later in September 2019, NICE recommended the use of this gene therapy product.[24,25] It is now expected that up to 100 patients currently living with this retinal dystrophy in the UK will have access to this treatment as soon as January 2020.[26]

More recently, in June 2019, ZYNTEGLO® gained approval by the EMA for the treatment of patients (aged 12 years and older) with transfusion-dependent β-thalassemia (TDT). Patients with this rare genetic disease, which is caused by mutations in the β-globin gene, have reduced or absent levels of haemoglobin, and require lifelong regular blood transfusions to lessen the chronic anaemia and, ultimately, survive.[27,28] ZYNTEGLO®'s therapeutic approach makes use of autologous CD34+ stem cells that have been genetically modified to contain the working β-globin gene. This authorisation for European marketing was the fastest assessment of an advanced therapy medicinal product (ATMP) to date, having also benefited from the EMA's Priority Medicines (PRIME) programme.[29]

Case study 3
Antisense oligonucleotide therapies offer new hope to patients with genetic disorders

Genetic sequencing is often critical in diagnosing rare diseases, many of which are fatal due to lack of available treatments. However, in the development of milasen, researchers at Boston Children's Hospital and Harvard Medical School designed, tested and manufactured an antisense oligonucleotide drug tailored to a particular patient within one year of first contact with them. The patient suffered from Batten disease, an inherited neurodegenerative condition with initial symptoms of deterioration in a patient's ability to speak, see and walk, which normally has no cure and is fatal. In sequencing the patient's individual genetic code, the researchers found a mutation that altered the assembly of an important housekeeping gene by creating a new, unwanted 'splice site.' In milasen, researchers designed an oligonucleotide to suppress the unwanted splice site and restore normal assembly of the gene, enabling the patient to produce functional proteins that had previously been lacking. While not a cure, milasen has led to reductions in the frequency and duration of seizures, and it is believed to be the first example of a personalised therapy developed and approved for a single patient.[30]

Deloitte's view

In the future, 'next gen' therapies will offer biopharma companies many opportunities for innovation. However, this will require significant shifts in how biopharma companies function. They will not only have to develop new capabilities, but also collaborate across all aspects of the biopharma value chain to ensure they can bring 'next gen' drugs to market efficiently and effectively. These shifts will also drive wider changes in the biopharma industry, including moving from intervention to prevention, or treatment to cure. If companies fail to shift their operating models to cope with these challenges, they risk continuing to drive an imbalance between invested costs and, despite high per-patient prices, cash inflows.

Reducing cycle times is key to the future of R&D

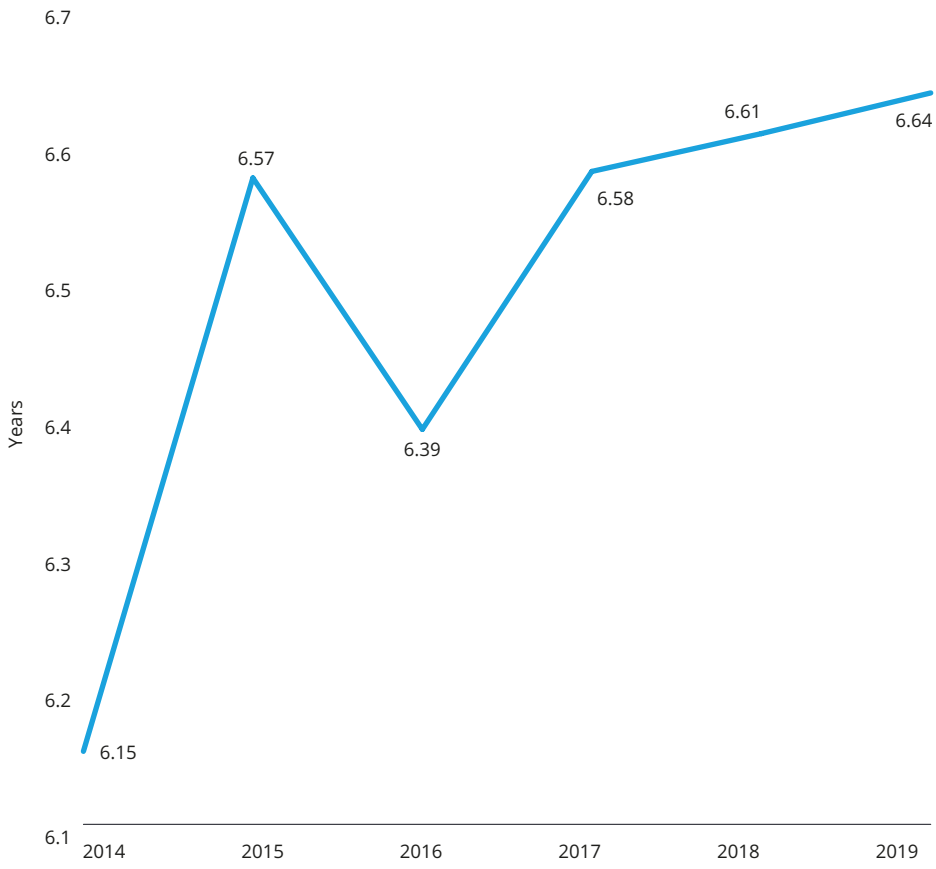
Across the industry, clinical trial cycle times have continued to grow (despite a small dip in 2014) (Figure 12). Companies today are taking longer than ever to bring new drugs to market, with complex protocol design and recruitment delays two key factors driving up average cycle times from Phase I to launch.

The ability to collect a greater volume and variety of data, including genomics, imaging, digital health data and patient reported outcomes, has expanded trial protocols which now include requirements to collect 'non-core data' for tertiary and exploratory data points, beyond what is needed for regulatory filings or to test primary study hypotheses.[31]

At the same time, biopharma companies have been finding it increasingly difficult to recruit patients that meet the selection criteria for their trials. Traditional recruitment mechanisms employed by biopharma have led to an 86 per cent failure rate of trials in meeting their recruitment timelines, and one-third of pivotal (Phase III) trials that require larger patient cohorts fail owing to enrolment issues.[32,33]

A shift in drug development efforts towards more scientifically complex therapy areas (such as oncology, immunology and rare diseases) has added to recruitment complexity. Often, key inclusion criteria involves identifying a biomarker, a measurable indicator of the severity or presence of disease. In recent years, close to 60 per cent of all trials and 80 per cent of oncology trials require some form of biomarker data as part of enrolment criteria.[34]

Figure 12. Average clinical cycle times, 2014-19 – original and extension cohorts (combined)



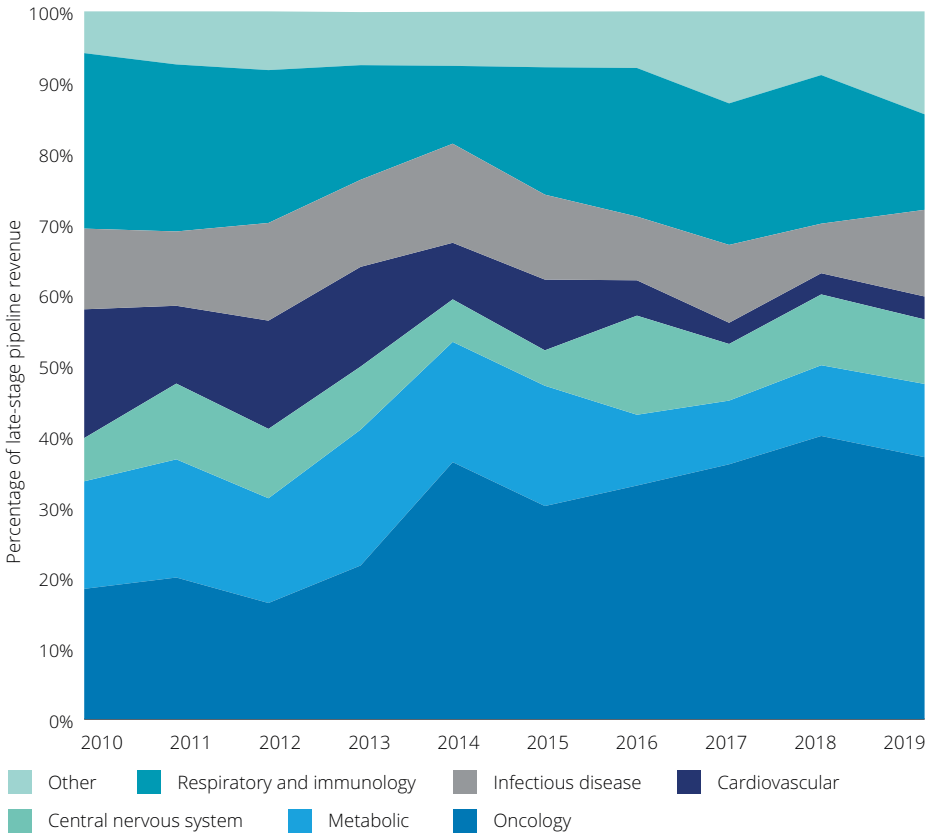
Source: Deloitte LLP, 2019

"Traditional recruitment mechanisms employed by biopharma have led to an 86 per cent failure rate of trials in meeting their recruitment timelines, and one-third of pivotal (Phase III) trials that require larger patient cohorts fail owing to enrolment issues."

The growing number of therapies targeted at the same biomarkers within a therapy or disease area has also resulted in even more competition for trial participants, slowing down patient enrolment. This is especially true in oncology, where GlobalData analysis reveals that industry-wide global clinical trials in immuno-oncology for 2008–2017 has increased at a CAGR of 17 per cent over the 10-year period.[35] Our analysis shows that an increasing share of the pipeline of our original cohort is focused on oncology, growing from 18 per cent in 2010 to 36 per cent in 2019 (Figure 13). Interestingly, our two cohorts are sponsoring an increasing share of industry wide oncology clinical trials (Figure 14).

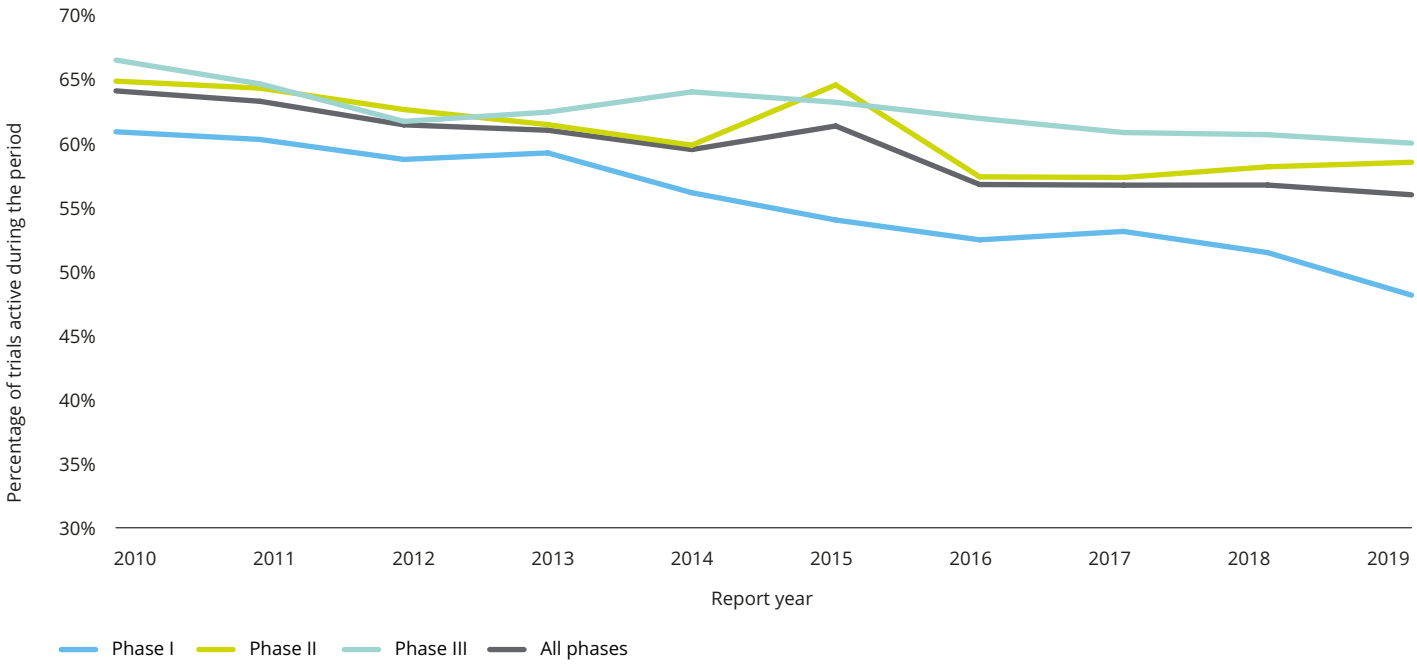
Figure 15 shows average cycle times for oncology are longer than other TAs generally, and has grown in 2019, likely attributed to increasing complexity of protocol design as well as increased competition to recruit eligible patients. Meanwhile, cycle times for other TAs, including central nervous system (CNS), infectious disease, metabolic disorders and cardiovascular (CV) have stayed relatively flat or declined.

Figure 13. Late-stage pipeline composition by therapy area, 2010-19 – original cohort



Source: Deloitte LLP, 2019

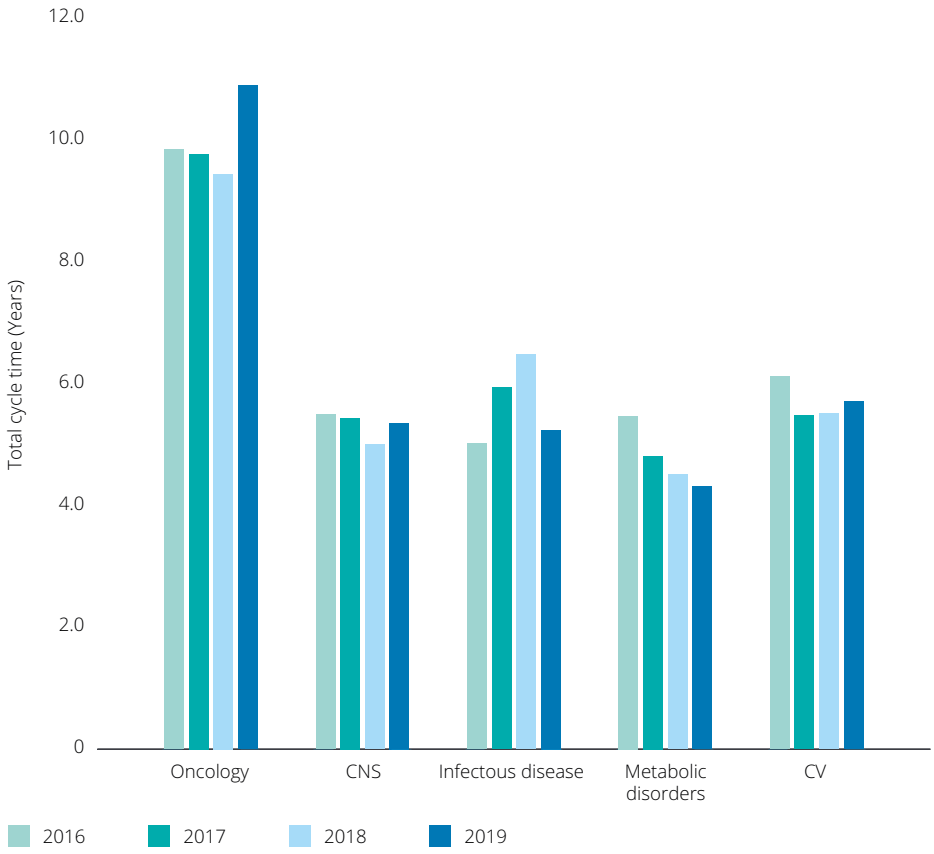
Figure 14. Cohort company sponsorship of oncology clinical trials, 2010-19 – original and extension cohorts (combined)



Source: Deloitte LLP, 2019

"In a bid to accelerate drug development and approvals, regional and local life sciences regulators have introduced a number of initiatives to improve cycle times."

Figure 15. Clinical trial cycle time by therapy area, 2016-19 – original and extension cohorts (combined)



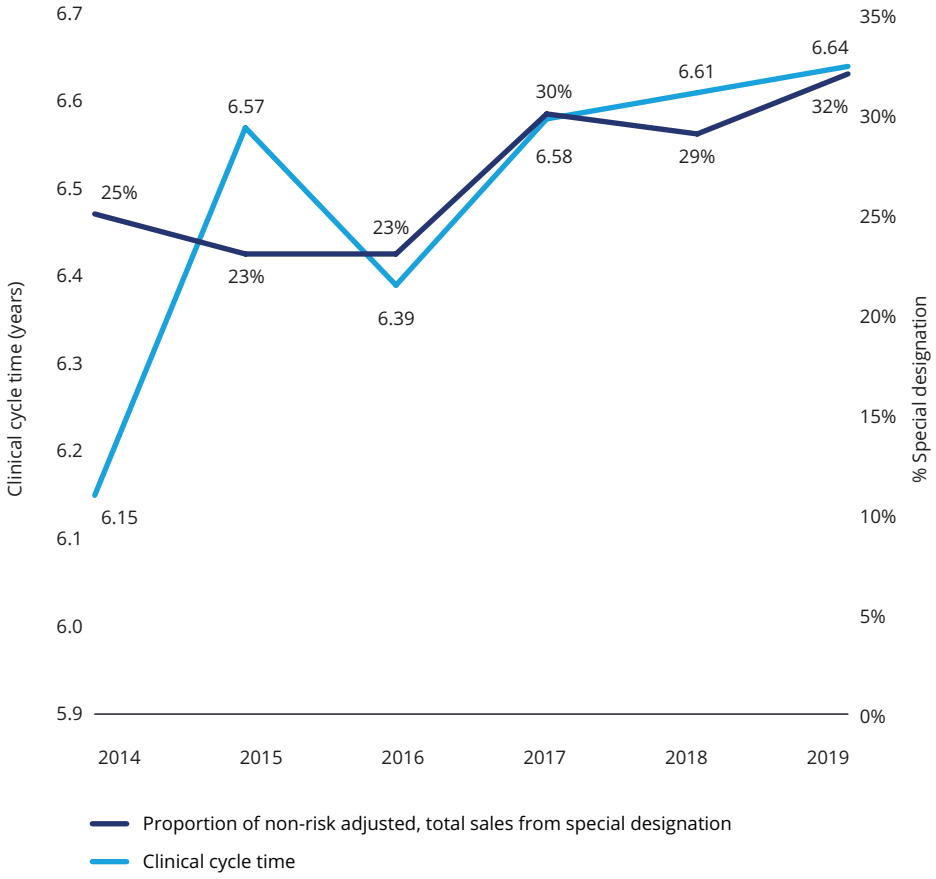
Source: Deloitte LLP, 2019

In a bid to accelerate drug development and approvals, regional and local life sciences regulators have introduced a number of initiatives to improve cycle times, including:

- in 2012, the FDA created the breakthrough therapy designation, allowing for accelerated approvals for therapies that are deemed to offer 'substantial improvements' over existing therapies, having expedited development and review[36]
- the FDA also established the Drug Development Tools Qualification Program in 2012 to evaluate methods, materials, or measures that have the potential to facilitate drug development, allowing for qualification of validated animal models, biomarkers, and clinical outcomes assessment tools[37]
- the 21st Century Cures Act, passed in 2016, further enables faster approvals by establishing a breakthrough designation for CAR-T cell therapies, and more flexible approaches to clinical trials, such as adaptive trial design and the use of RWE for label expansion[38]
- China has streamlined the approval process for new drugs, created procedures for expedited review of orphan drugs and has begun accepting data from foreign clinical trials in filings[39]
- in 2016, the EMA launched the priority medicines (PRIME) scheme, which provides early and enhanced support for the development of medicines that target unmet clinical need. In the first two years, 36 drug candidates across multiple therapy areas qualified for accelerated access.[40]

Despite such regulatory initiatives, clinical trial cycle times have continued to grow. Figure 16 shows that, although a growing percentage of the indications pursued by the original cohort received special designations, average cycle times continue to increase. Adoption of these approaches for almost a third of all pursued indications has not done enough to move the lever on cycle time overall, suggesting other, more fundamental approaches need to be considered when looking to alter this part of the productivity equation.

Figure 16. Clinical cycle time vs percentage of pipeline sales with special designations, 2014-19 – original and extension cohorts (combined)



Source: Deloitte LLP, 2019

Over the past few years, many companies inside and outside our cohort have adopted a number of approaches, including using study-level process optimisation techniques such as expedited contracting, improvements in the clinical trial management systems (CTMS) and risk-based monitoring. Some have begun to incorporate digital technologies, including artificial intelligence (AI) in the clinical trial process to expedite patient selection and enrolment, optimise protocol design, support site selection and capture patient reported outcomes or digital biomarkers (Figure 17).[41] Some companies are incorporating patient input into protocol design to reduce time-consuming protocol amendments and improve enrolment and retention rates. These approaches are relatively recent and have not yet impacted cycle times or the cost of development.

"Some companies are incorporating patient input into protocol design to reduce time-consuming protocol amendments and improve enrolment and retention rates."

Figure 17. Digital approaches to expedite clinical trials

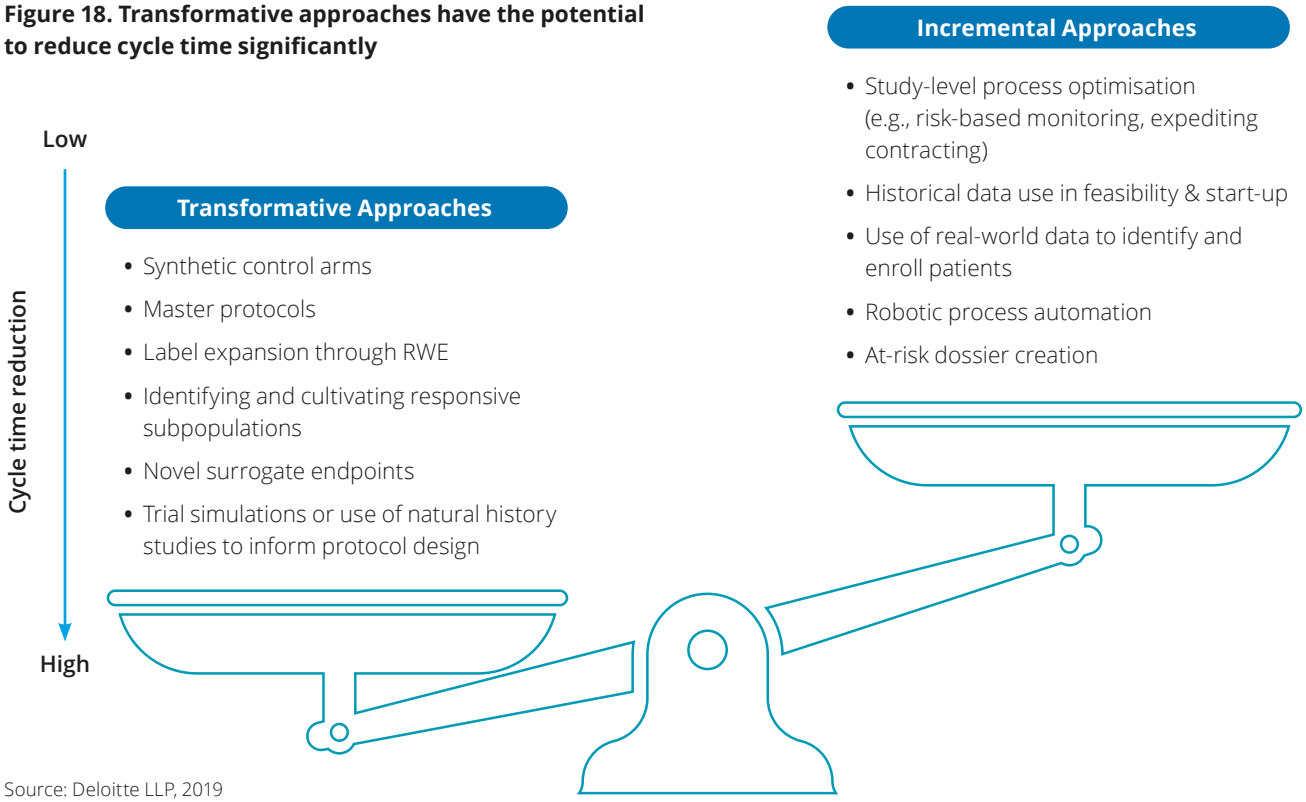
Source: Deloitte LLP, 2019

At present, companies are just beginning to explore the potential of AI for drug development. AI technologies can help improve filing efficiency, optimise the generation of suitable amounts of appropriate endpoints matched to regulatory requirements, and help the design, execution and administration of clinical studies. For instance, machine learning (ML) algorithms can proactively mine electronic health records (EHRs) and patient and clinical trial databases to identify potential matches between trials of relevance and specific patients, digitally enrolling patients and saving time on recruitment.[42] A few start-ups have already built systems using ML for automated trial matching (Case study 4).

Case study 4
Machine learning to enable patients to find the right trial

Antidote, through its platform, Antidote Match™, mines data from www.clinicaltrials.gov and uses ML along with minor human intervention to create structured eligibility criteria for single or multiple studies. The platform automatically generates a pre-feasibility questionnaire that translates complicated medical terms into easy-to-understand language for patients. Filling in the questionnaire enables Antidote Match™ to provide patients with a list of potential accessible trials that they are eligible for. Having completed over 100 recruitment projects, Antidote Match™ is the first clinical trial matching engine that uses structured eligibility criteria and AI algorithms to explore a patient's eligibility for one or many trials, thereby accelerating the recruitment process.[43]

Figure 18. Transformative approaches have the potential to reduce cycle time significantly



Source: Deloitte LLP, 2019

Increasing availability of disease specific research datasets, clinical genomics data and other real-world data (RWD), coupled with advanced analytics and AI, are aiming to power transformative approaches for cycle time reduction (Figure 18). These approaches can help companies make better decisions on product profiles, identify high-responder sub-populations, simulate clinical trial designs and support regulatory submissions. The use of natural history studies (information about the natural trajectory of a disease, in the absence of an intervention, from onset until either its resolution or the individual's death) in rare disease, synthetic control arms and collection of post-market real-world clinical data could reduce the need for some aspects of the clinical trial. A few companies are already:

- expanding label indications for on-market drugs without conducting trials
- building synthetic control arms from historical clinical data to reduce recruitment time and effort
- using novel surrogate endpoints for accelerated approval
- leveraging adaptive trials designs to allow quick and simultaneous evaluation of new drugs for multiple indications (Case study 5 and Case study 6).

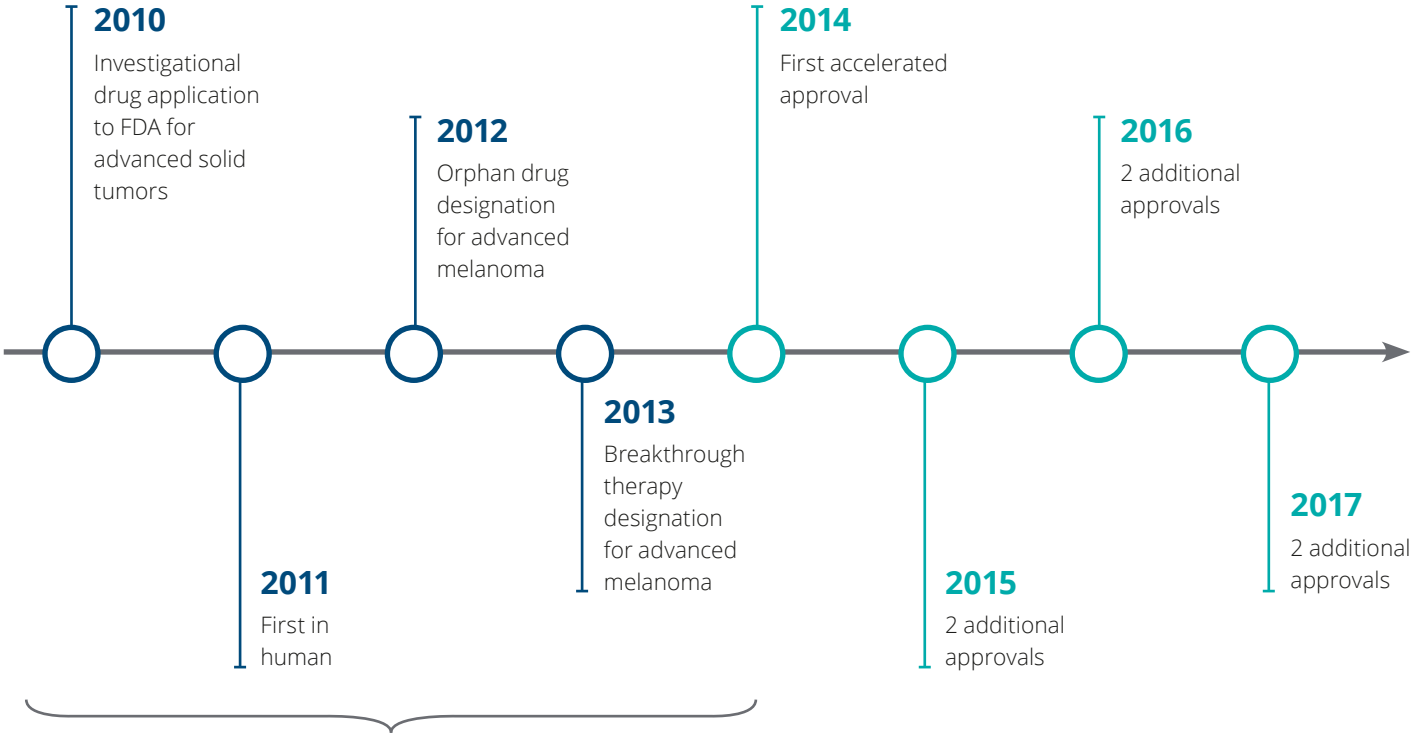
As explored in our November 2019 report *Intelligent drug discovery: Powered by AI,* AI will be also be an important accelerator of drug discovery and early stage development. AI technologies applied to historical trial data can investigate the potential relevance of already trialled drugs against comorbidities for drug repurposing.

Combining AI with other technologies such as organ-on-a-chip, 3D cell cultures and other cell models that replicate human biology *in vitro* could eventually eliminate preclinical testing. Furthermore, advanced computer modelling and simulations that test the safety of compounds (*in silico* trials) could eliminate the need for Phase I trials in healthy volunteers.[44]

Case study 5
Adaptive trial design to expedite time to market

Merck adopted a unique development pathway for Keytruda® (an immunotherapeutic), whose new drug application to initial approval took only four years, a radical reduction in development timelines. Using an adaptive trial design, Merck tested Keytruda®'s tolerability and impact on advanced solid tumours. It then added in melanoma and non-small cell lung cancer (NSCLC)-specific expansion cohorts for dose finding and efficacy assessments. Over the years, Keytruda® has been approved for several additional indications, including other forms of NSLC, melanoma and classical Hodgkin lymphoma.[45]

Figure 19. Approved indications for Keytruda® use in the US



Illustrative timeline. Not inclusive of all development and approval activity

Source: Deloitte LLP, 2019

Case study 6

Basket trial design leads to approval for first-in-class treatment for a rare cancer

Roche ran a tumour histology independent Phase II 'basket trial' to investigate Zelboraf® (vemurafenib) against BRAF–mutated cancers. These included colorectal cancer, multiple myeloma, Erdheim-Chester disease (caused due to abnormal multiplication of white blood cells) and others. The design involved seven patient cohorts to simultaneously evaluate efficacy of Zelboraf® either as a standalone or a combination therapy. Study results led to FDA approval for Zelboraf® as a breakthrough therapy for Erdheim-Chester disease in November 2017.[46]

Deloitte's view

Reducing cycle times is critical for biopharma companies. Continued collaboration with regulators, optimisation of study-level processes using digital technologies and other transformative approaches aimed at helping biopharma companies reduce cycle times may soon come to fruition. Oncology is one therapy area where these approaches are starting to be applied extensively. The impact of approaches such as automating data capture, drafting site and investigator contracts and digitalising standard clinical assessments on reducing cycle times will be evident in the next two to three years. This, coupled with new regulatory frameworks such as the FDA's Real-Time Oncology Review (RTOR), will enable data-driven R&D processes to speed up approvals and cycle times.

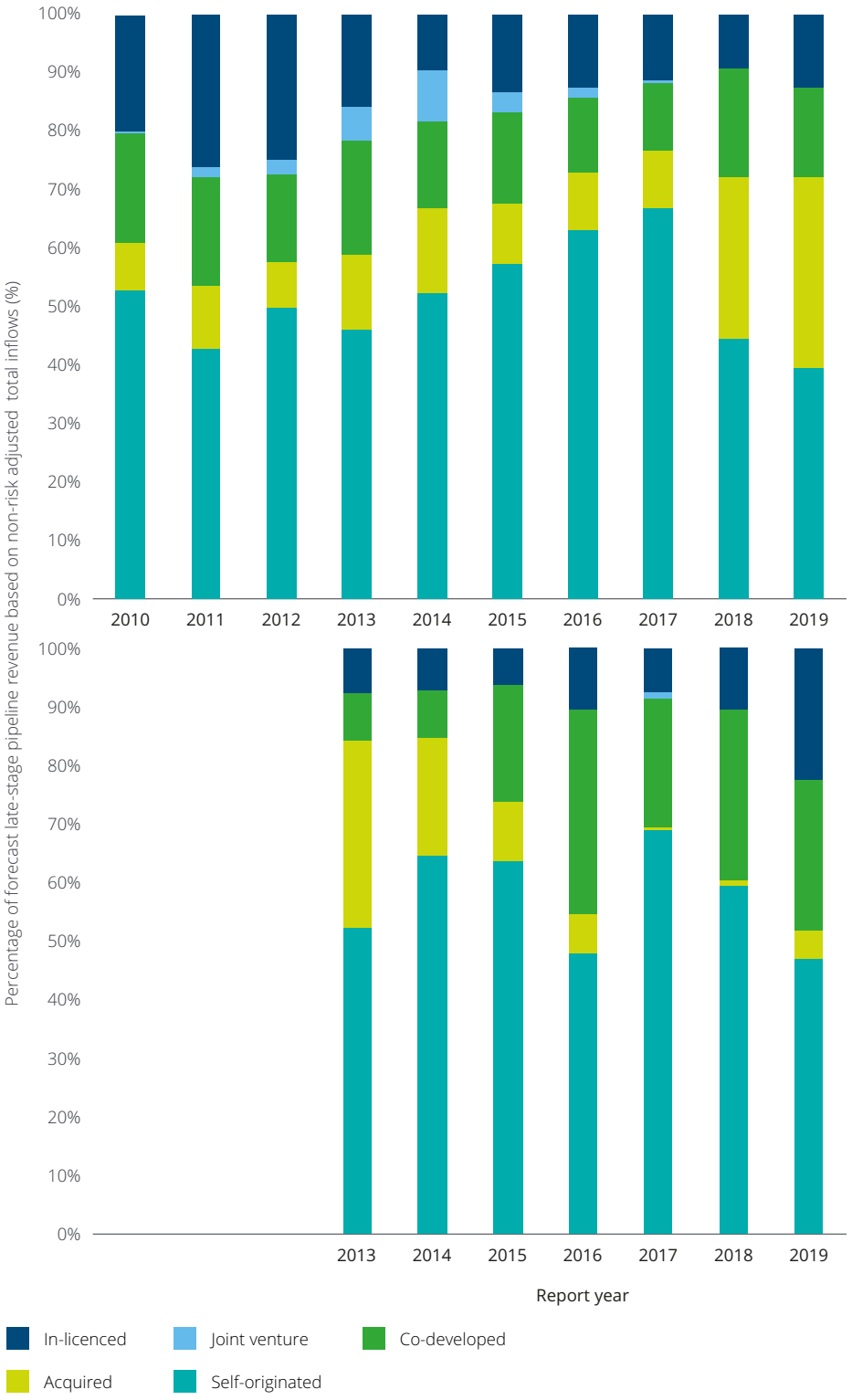
Sources of innovation for biopharma are changing

In 2010, close to half of the original and extension cohorts' late-stage pipelines were sourced through external innovation. This trend has fluctuated, with increasing and decreasing reliance on external innovation over the last 10 years. However, in the in the last two years, greater than 50 per cent of both cohorts' late-stage pipelines have been sourced externally.[47] Prior research suggests that externally sourced innovation launches at higher rates than industry benchmark, making this a desirable approach (Figure 20).

Notably, the original cohort is increasingly reliant on M&A as a source of innovation. This may be indicative of the challenges larger companies face in achieving growth on top of an already sizable revenue base, prompting them to seek consolidation to bolster pipelines and improve productivity through synergies. In contrast, the extension cohort is increasingly relying on in-licensing and co-development, suggesting more specialised companies are partnering to access capability as well as innovation.

The past few years have also seen the return of 'mega-mergers', highlighting the movement towards consolidation within the industry. There have also been a number of notable partnering deals, illustrating the high price companies are prepared to pay to access innovative pipeline products. This places emphasis on the need to extract value from these deals, which given the complexity and challenges involved, is not always straightforward.

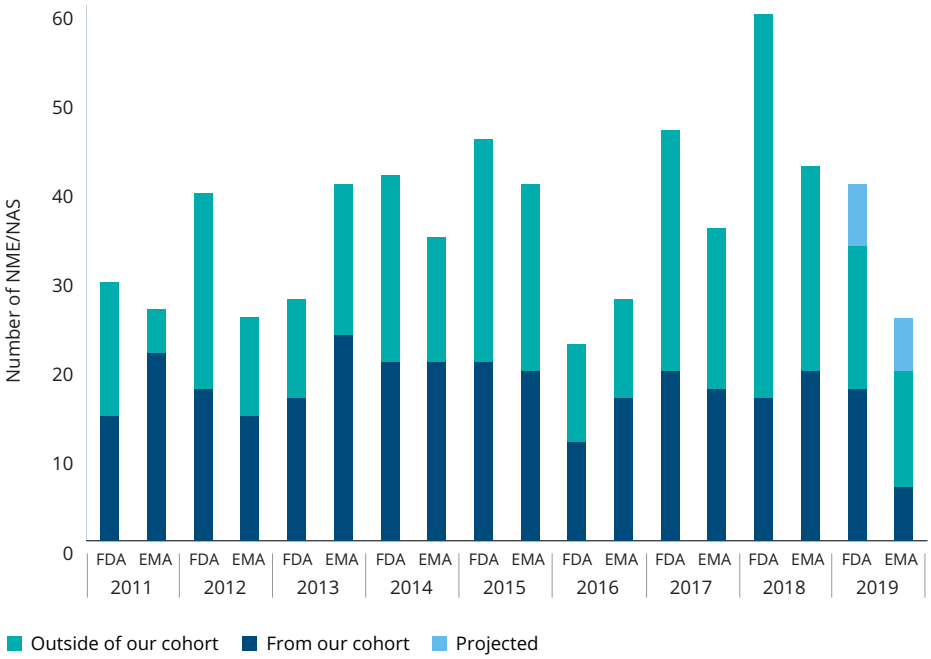
Figure 20. Proportion of late-stage pipeline sourced from internal and external sources, 2010-19 – original and extension cohorts



Source: Deloitte LLP, 2019

Moreover, an increasing proportion of new molecular entity/new active substance (NME/NAS) approvals have come from outside the cohort over the last 10 years (Figure 21). This suggests that novel drug approvals, which are more likely to command higher market share and pricing, are increasingly coming from smaller or newer start-up companies. These companies are increasingly less reliant on big pharma capabilities and capital to shepherd potential drug candidates through the drug development process. This trend raises questions around the sustainability of big pharma's current innovation model, and whether smaller companies may ultimately take an increasing share of the market by developing and commercialising products independently. Some smaller players have already seen success in the market (Case study 7 and Case study 8).

Figure 21. Number of NME/NAS approvals, 2011-19 – original and extension cohorts (combined)



NAS = New Active Substance, approved by the EMA. NME = New Molecular Entity, approved by the FDA. EMA date is based on CHMP opinions

Source: Deloitte LLP, 2019

Case study 7
Bringing the first RNAi therapeutic to market

In 2018, the FDA granted approval to Alnylam Pharmaceuticals to market the first RNAi (RNA interference) therapeutic, ONPATTRO™ (patisiran), for ATTR amyloidosis, a disease that leads to a build-up of toxic proteins in the kidney. While most drugs counteract the effects of harmful proteins, RNAi therapeutics disrupt mRNA (messenger RNA) by silencing the genes that transcribe harmful proteins. Since the discovery of RNAi in 1998, which led to the 2006 Nobel Prize in Medicine, several large biopharma companies attempted but failed to bring such RNA therapies to market. Despite several technological and financial roadblocks, Alnylam Pharmaceuticals was the first company to successfully develop and commercialise an RNAi therapeutic in the US.[48,49]

Case study 8
Launching the first oral medication for Fabry's disease

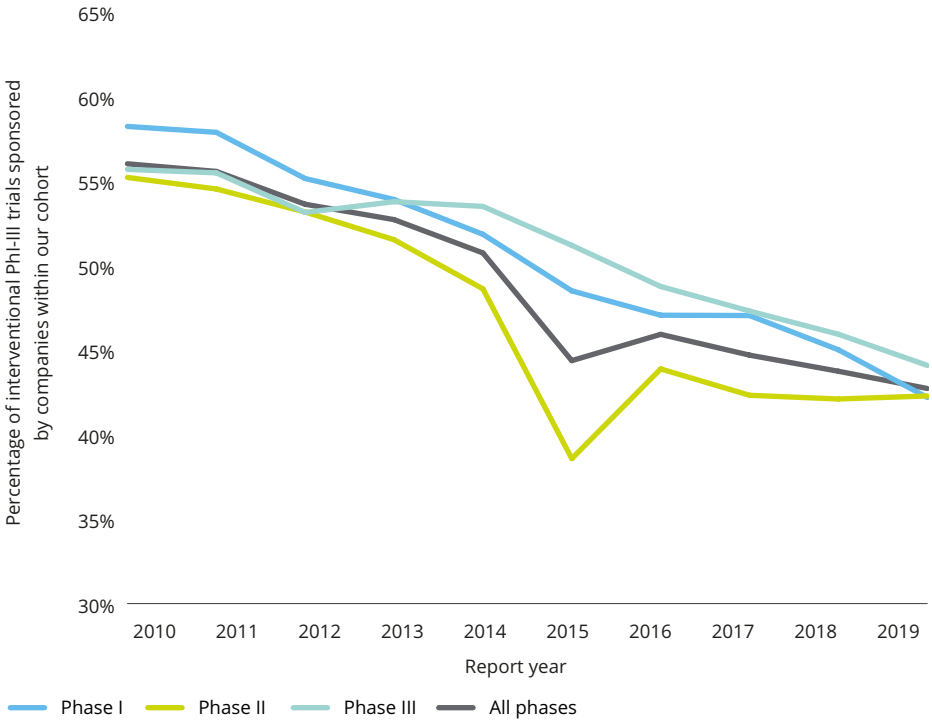
In 2019, Amicus Therapeutics received FDA approval to launch the first oral medication Galafold™ (migalastat) to treat adults with Fabry's disease. This disease occurs due to genetic mutations leading to an enzyme deficiency, which results in the accumulation of a harmful type of fat called globotriaosylceramide (GL-3) in various organs and tissues. Traditional treatment of Fabry's disease involves enzyme replacement therapy. Galafold™, on the other hand, binds to and stabilises dysfunctional enzymes, clearing the accumulated GL-3 from the body.[50]

This trend is unlikely to change, since companies from outside our cohorts are sponsoring an increasing proportion of clinical trials. In 2010, our original and extension cohort companies sponsored 56 per cent of all trials, which decreased to 43 per cent by 2019. Also, there has been sharp decrease (from 58 per cent in 2010 to 42 per cent in 2019) in the percentage of Phase I trials sponsored by our original and extension cohort companies (Figure 22).

Running clinical trials has traditionally required a significant amount of capital and scale, and smaller companies have relied on bigger biopharma companies as partners to provide these resources and capabilities. Furthermore, developing drugs that treat chronic disease in large populations required large, multi-site and multi-year trials. Today, the shift in focus towards new modalities targeting smaller populations, together with an influx of capital into the biotech market and increasing capabilities from the Clinical Research Organisation (CRO) industry, have enabled smaller companies to be able to sponsor clinical trials independently.

The shift in focus towards new modalities in disease areas with high unmet need has also changed the nature of clinical development programmes. Smaller companies focusing on disease areas, like rare and orphan diseases, are more agile and can pursue smaller patient populations or accelerated pathways. According to IQVIA, 'emerging biopharma companies, active in the fastest growing areas of oncology and orphan drugs accounted for 72 per cent of the 2018 late-stage pipeline activity, up from 61 per cent a decade ago.'[51] Strong capital markets and smaller scale clinical trials have likely contributed to the reduced need for these companies to partner or be acquired to develop their therapies.

Figure 22. Cohort vs non-cohort company sponsorship of clinical trials, 2010-19 – original and extension cohorts (combined)

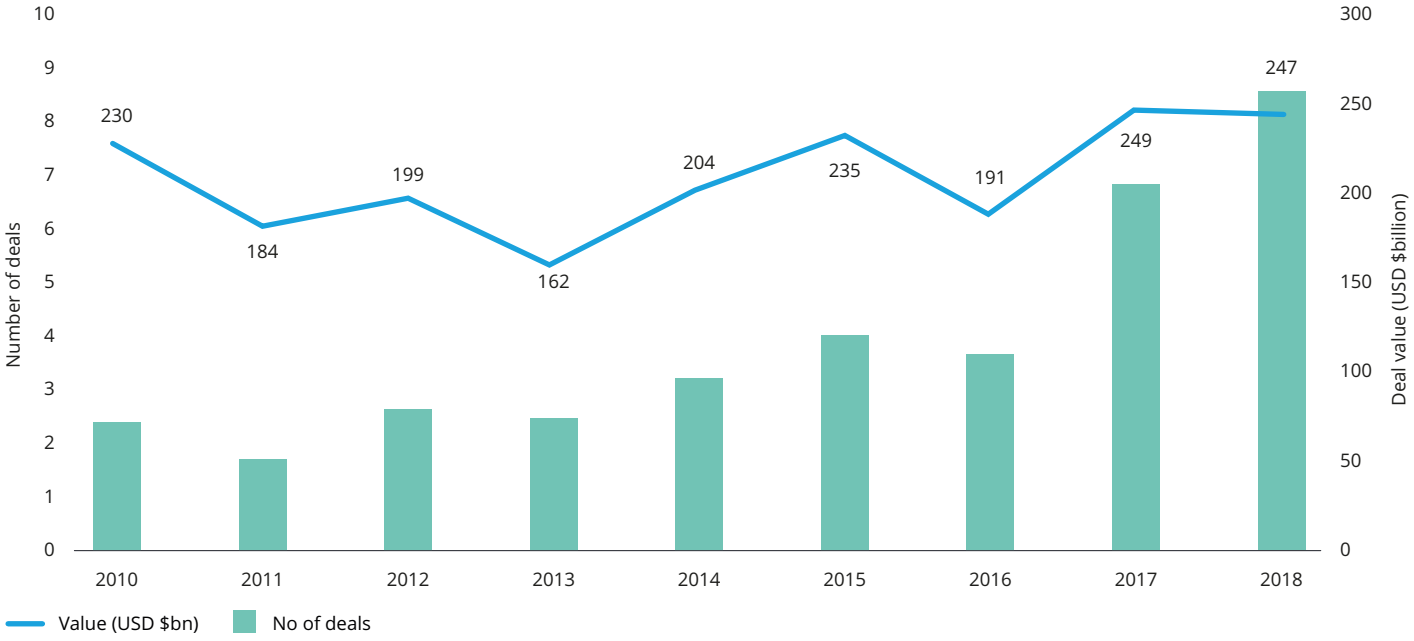


Source: Deloitte LLP, 2019

Deloitte's view

In recent years, our cohorts have shifted to buying or partnering to access innovation. This reflects the growing strength of entrepreneurial scientists, leading clinical research centres and visionary smaller companies as key originators of scientific innovation. In building new R&D models, biopharma has sought to replicate these innovation principles, but also added acquisition and partnerships to accelerate drug discovery. External innovation will therefore continue to be an important part of large biopharma companies' R&D strategies. However, this places additional emphasis on integrating and extracting the full value from the organisations being acquired. If they are not a sound strategic and operational fit, this can create barriers to realising the deal and overall R&D returns.

Figure 23. Value and volume of PE and VC investments in biotechnology companies, 2010-18



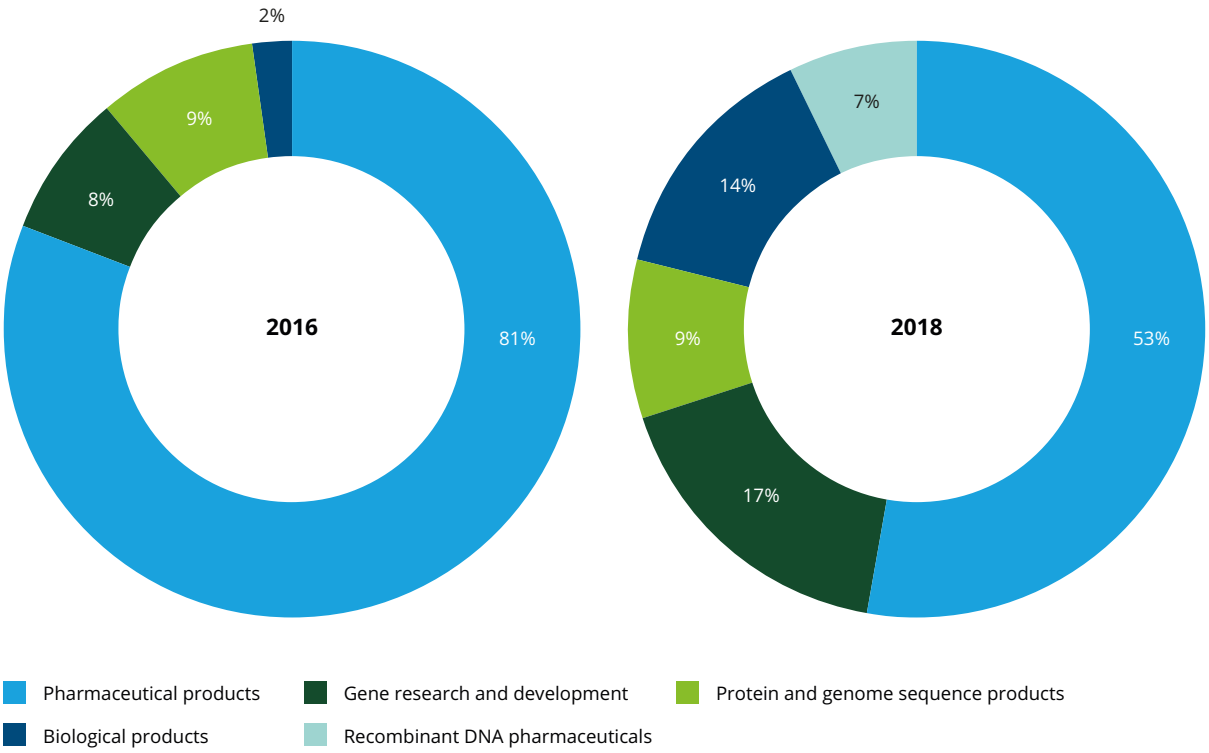
Source: Deloitte analysis of Capital IQ, as of 11th November 2019
*Please note this data includes VC and PE investments in the following: biological products, gene research and development, pharmaceutical products, protein and genome sequence products and r-DNA pharmaceuticals

Capital investment in biotech start-ups and clinical trial outsourcing is increasing

Since 2017, there has been a substantial increase in the total value of biotech deals, despite the number of deals staying relatively flat (Figure 23). Notably, part of the increase in private equity (PE) and venture capital (VC) investment went to companies focused on new modalities (Figure 24).

Over time, the size of the clinical trial outsourcing market has increased. There has been a consolidation of players in this space, with growing infrastructure and advancing capabilities. While lacking the infrastructure to conduct trials themselves, emerging companies may be channelling funds they have received into accessing CRO services.[52] In the past 12 to 18 months, a number of large CROs have launched new service lines targeting emerging biotech and biopharma companies.[53,54]

Figure 24. Increase in value of PE and VC investments in select areas



Source: Deloitte analysis of Capital IQ, as of 11th November 2019

Deloitte's view

Pharma are not the only investors seeking returns from early innovation – the rise in PE and VC investment in biotech companies indicates the value biotech companies are creating around cutting edge innovations in 'next gen' therapies. At the same time, outsourcing companies such as CROs and professional service firms are starting to build services to provide support to new biotech and biopharma companies to progress the development and even commercialisation of new drugs. This makes new biotech and biopharma companies less reliant on larger biopharma partners to commercialise therapies. Biopharma companies that seek to partner or acquire companies focusing on 'next gen' therapies are likely to face stiff competition and high valuations, further negatively impacting their returns on R&D. Some biopharma companies are increasingly turning to academic partnerships to access innovation earlier in the value chain and focus their internal capabilities. This focus of capabilities also relates to other collaborations, where the ability to bring together different skill sets helps to improve the chances of the partnership's success.

"Biopharma companies that seek to partner or acquire companies focusing on 'next gen' therapies are likely to face stiff competition and high valuations."

Shaping the future of biopharma innovation

An increasing amount of capital investment in biotech is driving higher asset and company valuations, and allowing emerging companies to pursue development into later stages. Will large cap biopharma companies be able to continue to buy innovation? Our cohort companies are likely to face threats from emerging biopharma companies focused on both scientific and digital innovation. In a future of health driven by shared, radically interoperable data, empowered consumers and scientific breakthroughs, biopharma companies will need to develop core capabilities that are entirely different from today.[55] These capabilities are likely to be focused around the need to access, analyse and interpret large datasets, including deploying AI technologies. This will require a fundamental shift in the biopharma R&D model.

The impact of digital transformation on R&D, including the rise of AI for drug discovery companies

Digital technologies are starting to transform how biopharma companies approach clinical development by incorporating insights from multiple sources of data, providing an opportunity to improve the patient experience, enhance clinical trial productivity, and increase the amount and quality of data collected in trials. However, digital transformation is not just about technologies, platforms and advanced analytics; it is a way of doing things differently. Consequently, adopting a digital mind-set is a new business imperative.

A comprehensive digital R&D strategy can be critical to enable companies to move and process large amounts of data effectively, to make data-driven scientific and business decisions quickly and accurately, and to generate evidence in support of future product value propositions. This will require new capabilities, new skill sets and new partnerships.[56]

Deloitte's recent report *Intelligent drug discovery: Powered by AI* identified significant growth in the AI for drug discovery landscape, which comprised 170 AI companies, 50 corporations, 400 investors and 35 major R&D centres in July 2019. The market for AI in drug discovery increased from $200 million in 2016 to $700 million in 2018 and is expected to reach $20 billion in the next five years.

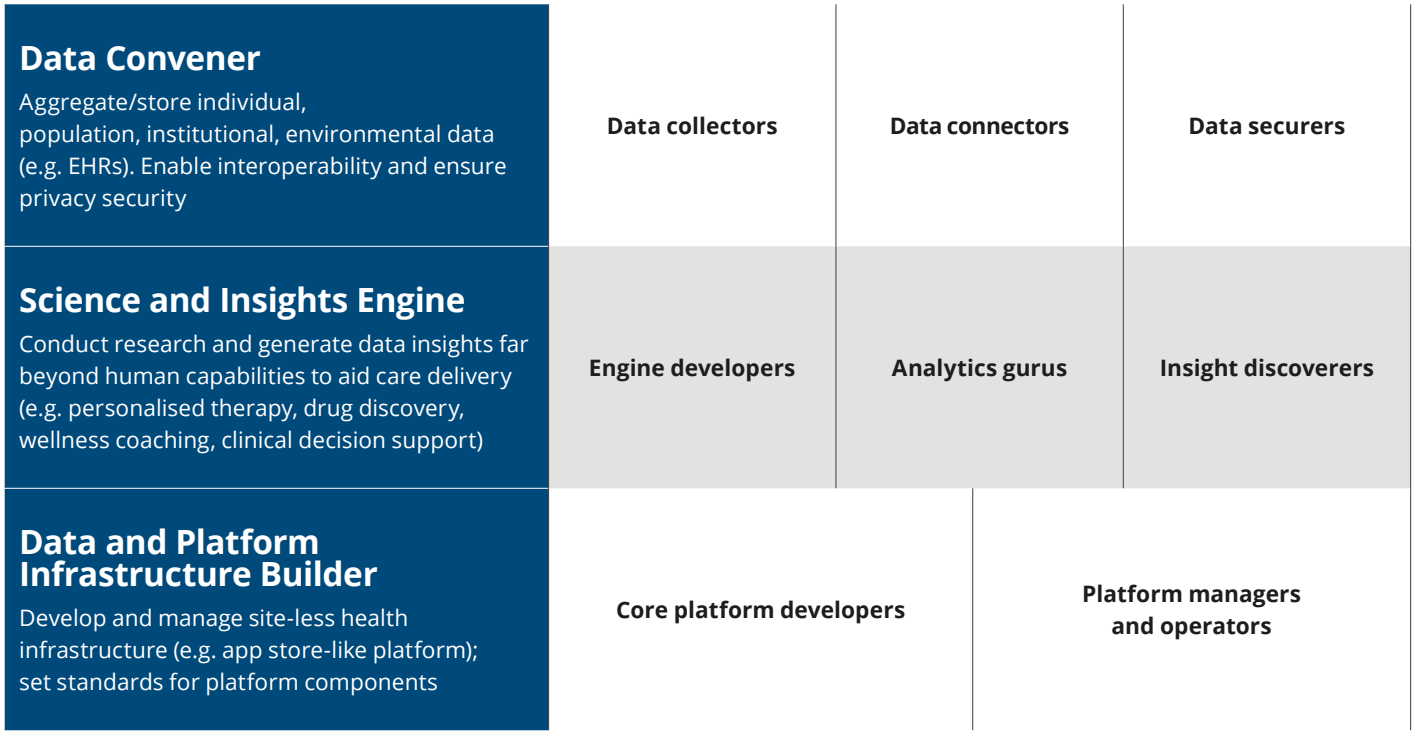
The report highlights the fact that AI-driven drug discovery companies are utilising vast amounts of biopharma research data, including RWD, to move more targeted new drug candidates into clinical trials, in some cases in months rather than years.[57,58]

Some AI for drug discovery companies are building their own pipeline of products and seeking to bring products to market independently. This will become increasingly possible with an influx of AI-driven drug development capabilities, both within CROs, as well as from start-ups. Indeed, most large biopharma, including our cohort companies, have started to partner with AI start-ups to support drug development. We conclude that these companies will be better prepared to compete in the future and those that do not pursue these capabilities are likely to be left behind. Moreover, AI solutions, if adopted at the drug-discovery stage, have the potential to kick-start the productivity of the entire R&D process.[59]

Deloitte's view

AI is only one strand of innovation that companies are pursuing as part of their digital transformation of R&D. Digital processing of large genetic, phenotype and medical data creates the potential for computational drug discovery and development, with new analytical models and AI improving cycle time and technical chance of success. Other strands of innovation include earlier partnering, new operating models to support cell and gene therapies, digital therapeutics and interventions focused on prevention and disease modification rather than symptomatic management or acute intervention. Adopting these approaches will be an imperative for biopharma companies.

Figure 25. The three main business archetypes that are likely to apply to biopharma in the Future of Health



Source: Deloitte analysis

The 'Future of Health' and its implications for biopharma

As innovations in medical technology enable us to diagnose genetic and genomic–based diseases much earlier and more precisely, there will be a shift to curative therapies, targeted at much smaller populations. For the rest of the population, there will more customised medicines, driven by the availability of large, real-world datasets informing subpopulations of high- and low-responders. The majority of treatments will be combinations of generics and biosimilars, using customised doses that drastically improve patient outcomes. There will also be a much greater use of non-pharmacological interventions, such as digital therapeutics and microbiome-based therapies for treating or preventing conditions such as obesity, pain, depression and cognitive decline.[60]

The past 10 years of decline in IRR illustrates quite starkly that the biopharma industry needs new models of R&D. Furthermore, revenue-impacting disruptions from technology, smaller biopharma and biotech companies are happening right now, requiring an urgent response. This, together with the changes brought by the future of health, means that biopharma companies will have to think radically differently about what type of company they want to be, and where and how they want to play. The growing number of rich datasets, and advances in genomics, analytics and science more generally, will require every biopharma company to make hard decisions on what type of R&D model will be most appropriate for their future sustainability.

For health care more generally, Deloitte has identified 10 different data and information archetypes that will define the future of health. For biopharma, we believe that the most likely archetypes are a combination of data conveners, science and insight engines, and data and platform infrastructure builders. The key questions for biopharma are whether to specialise or integrate the different archetypes, and what this means for their R&D model, especially around the science and insights engine. Furthermore, can biopharma use these archetypes to increase their returns and the affordability of medicines (see Figure 25).

Regardless of the archetypes that each company pursues, there are fundamental capability investments associated with new R&D models that need to be adopted aggressively to succeed in this new environment. Many companies have begun to make significant investments and develop partnerships to acquire the skills and talent that are needed, including highly trained, specialist data experts and experts in AI and computational biology. The specific implications of the Future of Health for biopharma R&D are as follows:

- R&D data-driven insights will enable companies to develop customised treatments by identifying which therapies will work in which patients. For example, *in silico* analysis will predict drug efficacy using data available on chemical drug features and genomic make-up. Synthetic trials with near perfect information and the application of advanced analytics will shift drug discovery from bench to *in silico*

- advanced analytics (ML, NLP, etc.) and robotic process automation will enable end-to-end automation of R&D, reducing timelines significantly. This will also shift the traditional cost of drug development from large-scale clinical trials to the storage and computation of large datasets to develop highly effective personalised therapies

- R&D costs will shift from traditional discovery and trial execution (requiring extensive amounts of clinician involvement and challenges in patient recruitment and retention) to a process driven by large RWE health datasets, investments in interoperability, and advanced computing power and cloud data storage

- sophisticated drug development algorithms will inform personalised, active pharmaceutical ingredient (API) combinations that can be manufactured and delivered directly to the consumer by pharmacies with, for example, 3D printing customising APIs to deliver personalised therapies

- scientific breakthroughs, including stem cells, nanobots, biome sensors, and others, will occur at an exponential pace, building on the insights derived from radically interoperable data, with industry and new incumbents disrupting the market and transforming clinical trial structures, timing, including increased participation from the 'crowd'

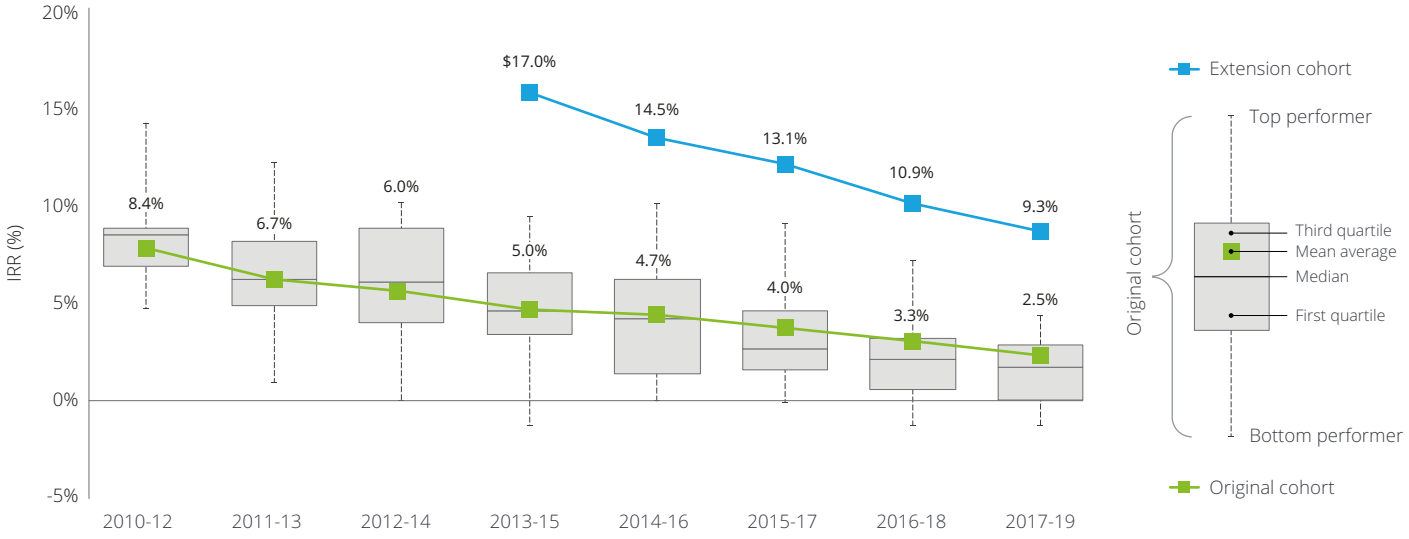
- as drug targets shift from symptom management and disease modification to curative and preventative approaches, mass-market maintenance therapies will decline. For example, DNA-based insulin gene therapy will likely eliminate Type 1 Diabetes, and hyper-tailored therapies, early intervention and enhanced adherence should lead to a drop in volume of units and increases in prices.[61]

Deloitte's view

While we maintain the 'tempered optimism' from our first *Measuring the return from pharmaceutical innovation* report about biopharma's future and that biopharma companies can reverse the past decade of decline shown in our analysis, this will require radical decisions about future business and operating models. We believe that advances in science and technology will find solutions to the most pressing unmet needs of patients. However, the challenges around reducing R&D costs, declining expected peak sales, expanding regulatory requirements and more demanding reimbursement hurdles will remain. With data and information the life-blood that sustains R&D, we envisage some biopharma companies will become data organisations, while others will transition to a leaner, more focused, science-based model aligned to innovation clusters and a growing revenue stream from speciality products and biologics. Data, technologies and new science will create new discoveries, cures and customised medicines, brought to market by changing regulatory environments and greater R&D precision. The future is better than today. We just do not know it yet.

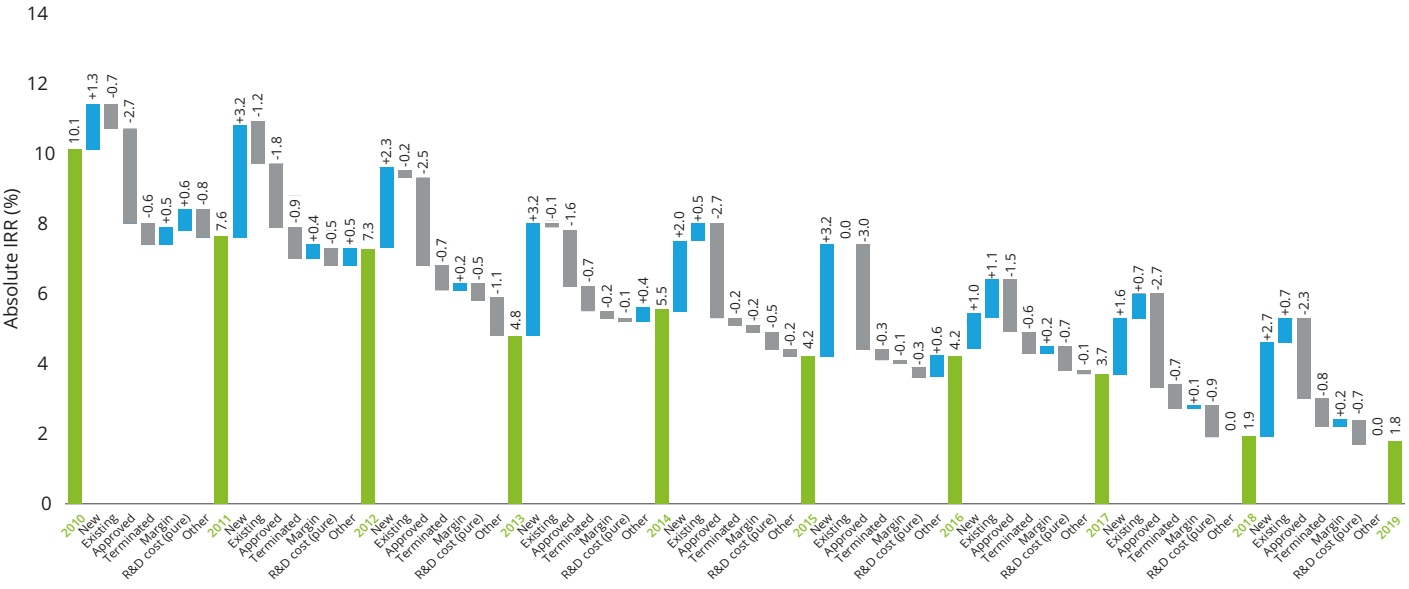
Appendix

Figure 26. Three-year rolling average returns on late-stage pipeline, 2010-19 – original and extension cohorts



Source: Deloitte LLP, 2019

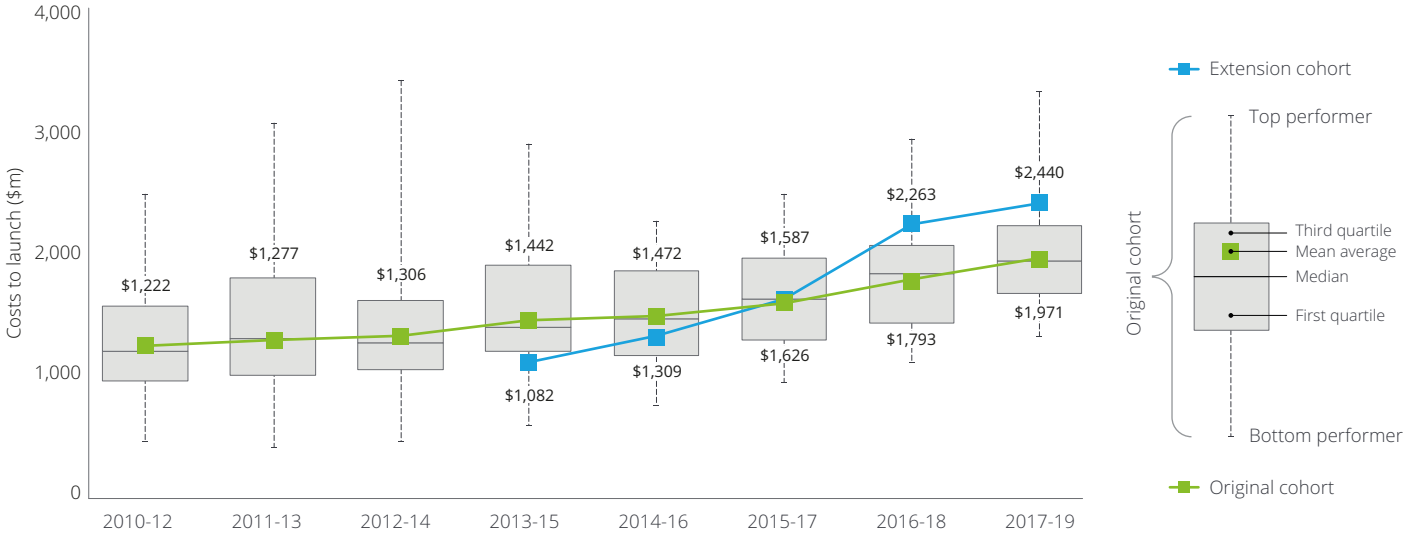
Figure 27. Year-on-year drivers of change in IRR, 2010-19 – original cohort



Source: Deloitte LLP, 2019

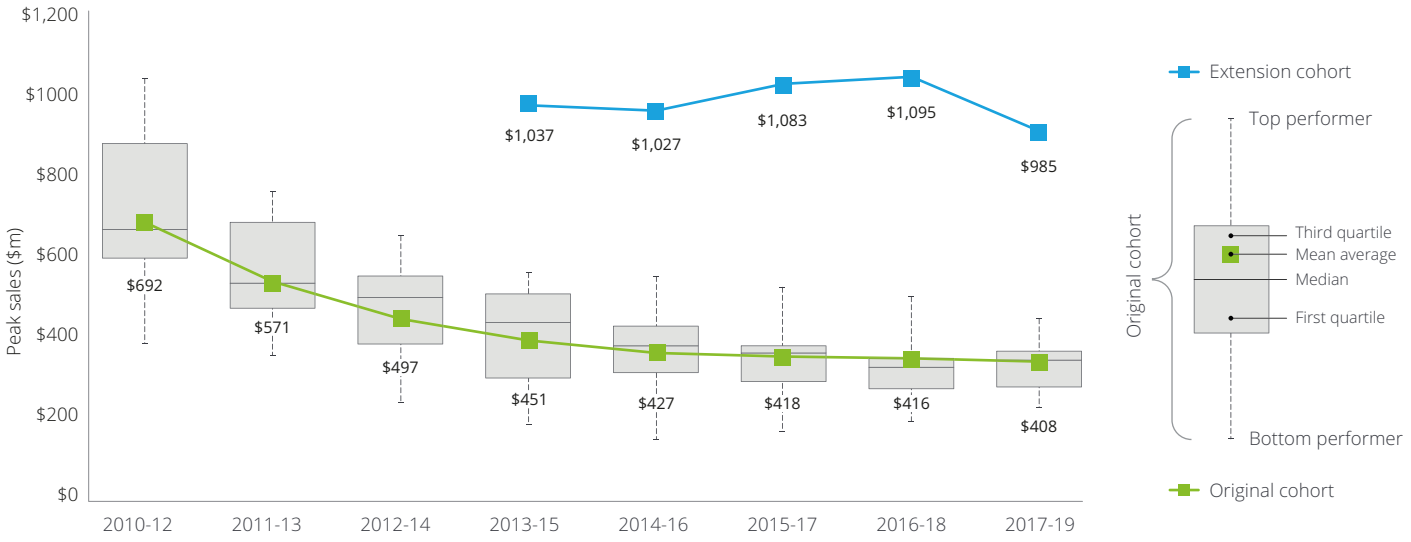
Due to rounding, numbers presented throughout this document may not add up precisely to the totals provided, and percentages may not precisely reflect the absolute figures.

Figure 28. Three-year rolling average R&D cost to develop an asset from discovery to launch, 2010-19 – original and extension cohorts



Source: Deloitte LLP, 2019

Figure 29. Three-year rolling average peak sales per pipeline asset, 2010-19 – original and extension cohorts



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We would like to acknowledge the significant contribution of the following people to the analysis, research and drafting of this report, without which this report would not have been possible: Kevin Dondarski, Pavithra Rallapalli, Evelyn Chu, Hawo-Kiin Ali, Nick Wright, Matthew Thaxter, Chloe Ambery, Youcef Mahfoufi, Andy Bolt, Dave Nestor, Carmen Jack and Pratik Avhad.

GlobalData Contributors
We would like to acknowledge the contribution of Cynthia Brisac (GlobalData Pharma Consulting) and GlobalData's Therapy Analysis and Database teams

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Designed and produced by 368 at Deloitte, London. J19037