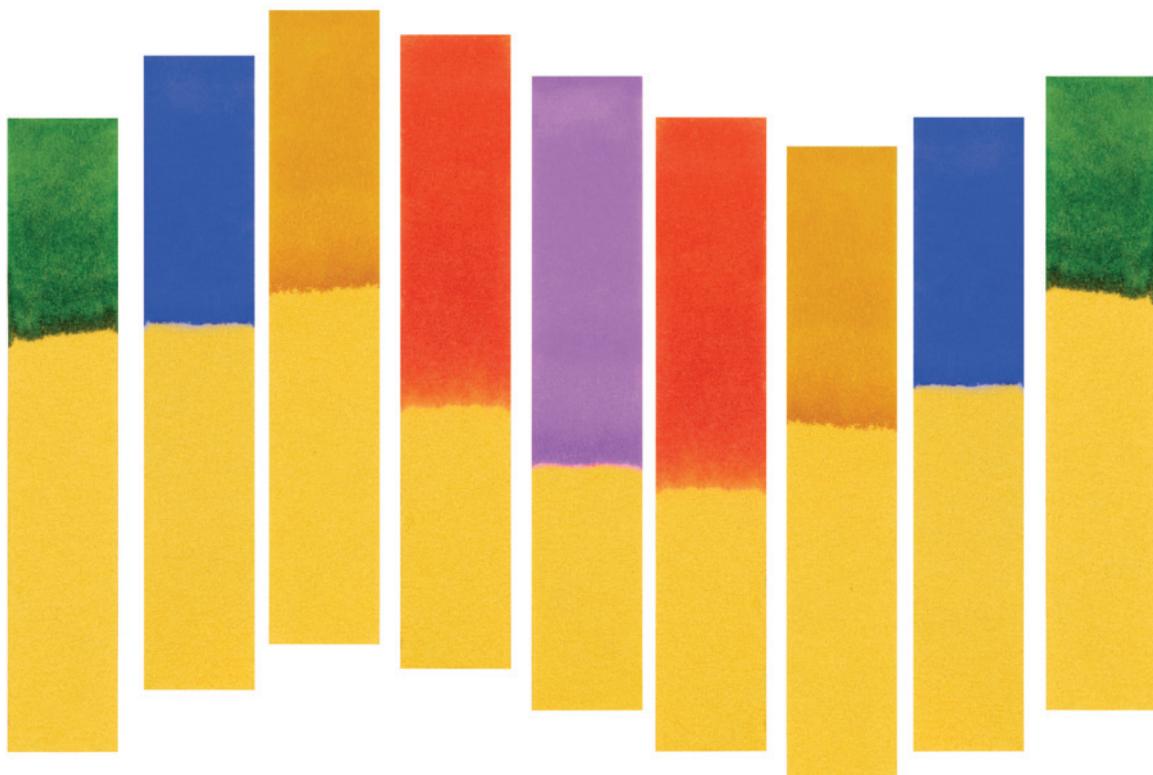


Measuring the return from pharmaceutical innovation 2013 Weathering the storm?



Contents

Foreword	1
Executive summary	2
Part 1: Peer benchmarks	3
Part 2: Strategies for transforming R&D returns	13
Part 3: Conclusions	17
Appendix 1: Methodology	18
Notes	27
Glossary	28
Contacts	30

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Foreword

Welcome to this Deloitte LLP report, the fourth in an annual series exploring the pharmaceutical industry's performance in generating a return from its investment in new product innovation.

Since 2010 Deloitte LLP, in association with Thomson Reuters, has been quantifying the return on investment that 12 of the leading life sciences companies might expect to achieve from their late stage pipelines. These pipelines comprise assets that are either currently in Phase III, filed or submitted, and therefore expected to launch within the next three to four years.

The global economic environment continues to prove challenging with relentless downward pressure on healthcare budgets and constraints around market access and pricing. At the same time, research and development (R&D) leaders are tasked with originating or acquiring high quality assets to fuel development pipelines. Despite these hurdles, this year's analysis identifies that, over the longer term, the leading companies are moving in the right direction – pulling promising new assets into pipelines and successfully commercialising medical innovation. While the trajectory is correct, the pace of industry transformation must accelerate significantly to achieve sustainable and compelling levels of return from the investment in innovation.

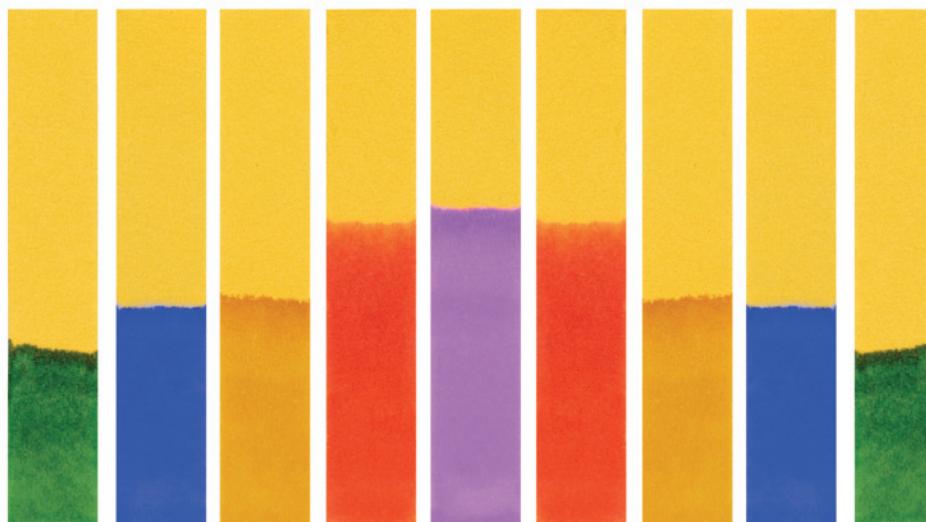
This year's findings should continue to provoke discussion around R&D return on investment. We hope you will find the report thought-provoking and insightful and welcome your feedback and comments.



Julian Remnant
R&D Advisory Partner,
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John Cole
Solutions Director, IP & Science,
Thomson Reuters



Executive summary

While pipeline flow has remained intact, the total projected value of late stage pipelines has declined from \$1,369 billion to \$913 billion since 2010.

Over the course of the four years of this analysis, the cohort of 12 companies has launched 105 products and transferred \$770 billion of projected value into their commercial portfolios to the benefit of patients. Over the same period, the research and development (R&D) engines of these companies have pulled 167 assets into late stage development, with a total risk-adjusted value of \$819 billion.

Despite these positive indicators, the projected return on investment in innovation that the cohort's late stage pipeline is expected to deliver has continued to decline across the four years, from 10.5 per cent in 2010 to 4.8 per cent in 2013. The cohort result hides wide variations in company performance. Some companies are achieving higher rates of return and others are struggling to safeguard growth.

While the number of assets in company late stage pipelines has remained stable since 2010, indicating that pipeline flow has remained intact, the total projected value of late stage pipelines has declined from \$1,369 billion to \$913 billion. Since 2010, specific aspects of the economics of value generation (cash outflows versus cash inflows) that are holding back R&D returns at a cohort level are:

- a 43 per cent reduction in projected peak sales per asset from \$816 million to \$466 million, likely due to the impact of austerity measures and the industry's need to calibrate their innovation investments with the needs of payers earlier and more consistently
- the adverse impact of terminations, late stage failures continue to take too much value out of the cohort's pipeline, amounting to \$243 billion over the four year period
- an increase in the level of overall R&D investment as the anticipated impact of R&D cost saving programmes have yet to be realised in full. The cost to develop and launch a new medicine has increased 18 per cent to \$1.3 billion over the four year period

- phasing of R&D investment, assets are spending longer in complex and expensive late stage development, particularly between 2012 and 2013, and total development time has increased from 13.2 years to 14 years. Companies are taking longer to collect more evidence and to decide whether to progress assets through to the next phase of development.

A detailed analysis of movement in year-on-year returns is more revealing in terms of drivers of performance. More specifically, 2010-11 was a period of successful launches, 2011-12 was a period of bringing new assets into the late stage pipeline and 2012-13 was a year of balance – value from new assets balanced value transferred to the commercial portfolio.

Overall, R&D organisations are commercialising effectively, this is particularly apparent over the last year, but they are failing to match this level of performance in other drivers of R&D returns, for example cost containment and rate of innovation. Companies need to maintain their current trajectory in terms of moving compounds into the late stage pipeline and on to commercialisation. However, the pace of change in factors underlying the economics of R&D needs to accelerate for the sector to achieve a sustainable level of returns.

This report has identified three key areas where business leaders should focus to drive improvements in R&D returns:

- maximising the value of science
- preserving and developing talent in R&D
- harnessing the power of analytics to enhance R&D decision making.

Although the adverse global economic climate appears to be easing, market conditions are likely to continue to prove challenging for life sciences companies. Payers will continue to apply downward pressure on price, with premium pricing reserved for the few, truly innovative drugs that can demonstrate improvements over existing therapies. Market access hurdles and demands for better outcomes data will continue to present the industry with a challenging environment in which to drive improved R&D returns.

Part 1: Peer benchmarks

Dynamic returns

Assessment of dynamic returns allows the impact of key drivers of change in life science research and development (R&D) performance to be measured for a given time period. There are a number of change drivers included in this report:

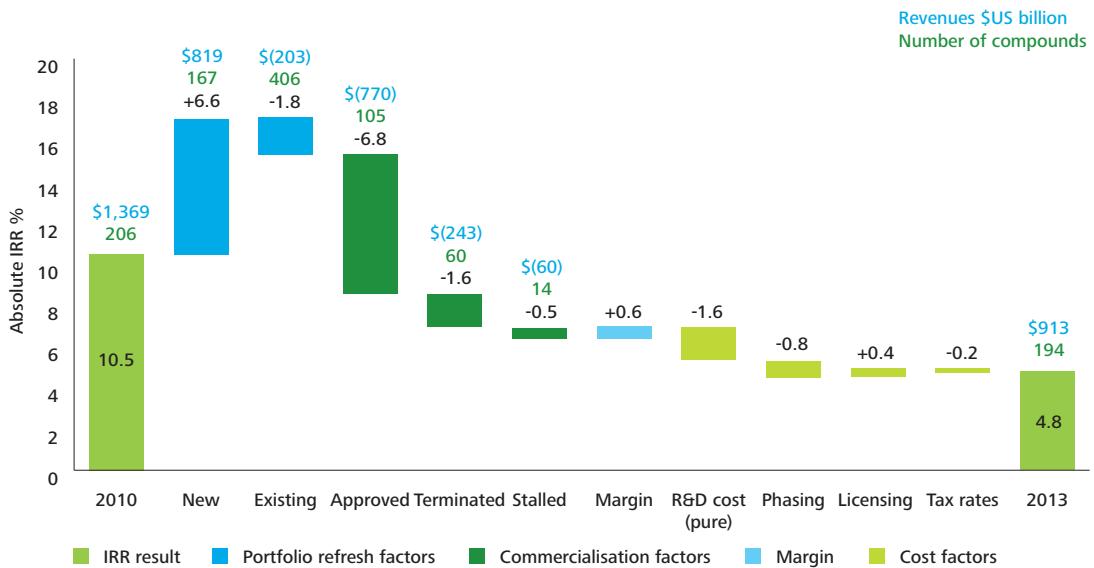
- new compounds entering the late stage pipeline in the year ending April 30 for each year under investigation (2010, 2011, 2012 and 2013)
- changes in revenue forecasts of existing late stage pipeline drugs – those drugs in the late stage pipeline in the previous year
- approvals due to commercialisation of late stage pipeline drugs
- terminations either through company-originated termination or unsuccessful application for marketing authorisation
- stalled compounds not officially terminated but unlikely to launch, for instance due to the publication of unfavourable clinical trial data
- margin and cost factors such as changes in R&D costs and tax rates.

This report defines, measures and assesses the impact of each of these drivers for the same cohort of companies over a cumulative four-year time period, 2010-13 (Figure 1).

Over the past four years R&D returns have steadily declined

For the period 2010 to 2013, the positive impact of revenues from new compounds entering the late stage pipeline was sufficient to fill the gap left by the successful commercialisation of assets as they launched. However, the level of pipeline replenishment has been insufficient to offset commercialisation along with the cost of failure (terminated and stalled compounds) and reductions in forecasts for existing compounds. Additional downward pressure from operational drivers such as pure R&D cost (R&D expense incurred to progress the basket of assets into the late stage pipeline), phasing (amount of time and investment incurred in late stage pipeline development) and tax rates was not balanced by improvements in operating margin and licensing costs.

Figure 1. Drivers of change in IRR, 2010–13



See glossary for definitions of factor used in this figure
Source: Deloitte LLP and Thomson Reuters research

Three year-on-year time periods (2010-11, 2011-12 and 2012-13) were also analysed to identify trends in dynamic returns (Figure 2).

Number and value of late stage compounds

Over the past four years, the number of late stage compounds within the cohort has remained stable at around 200 (Figure 2). The total forecast inflow of these assets declined from \$1,369 billion in 2010 to \$913 billion in 2013.

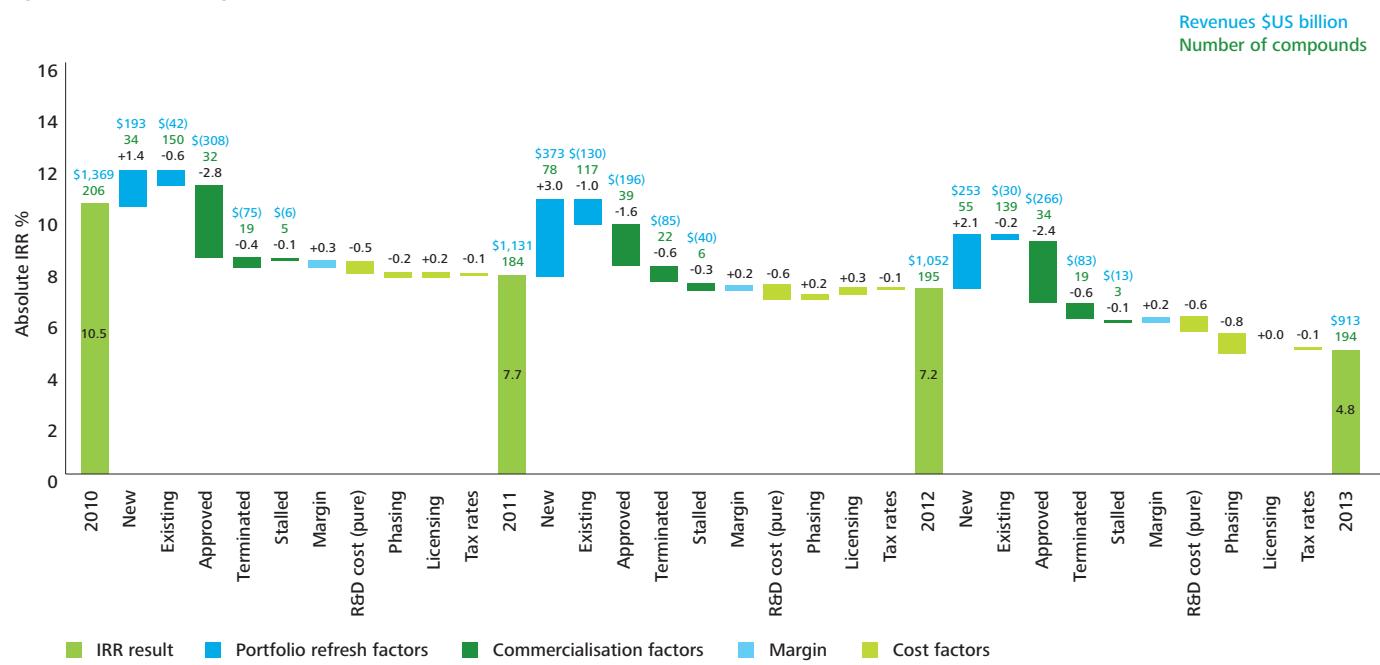
The increase in movement of compounds seen in 2011-12 was not maintained in 2012-13. While the number of approvals and terminations declined from 39 to 34 and 22 to 19, respectively, the number of new compounds entering the pipeline fell from 78 to 55, leading to an overall reduction in compound movements.

Trends consistent for the time periods 2010-11, 2011-12 and 2012-13

Comparing year-on-year changes in returns highlights some key trends consistent across the three time periods. New compounds entering the pipeline continued to provide significant uplift to year-on-year returns. However, each year this uplift was insufficient to balance the transfer of late stage pipeline value to the commercial portfolio when combined with losses due to terminations, stalled compounds and reductions in revenue forecasts for existing compounds.

Minor improvements in operating margins and reductions in licensing costs had a positive impact for each of the three time periods considered. Increases in overall R&D cost and tax rates resulted in a small, negative impact on year-on-year returns.

Figure 2. Drivers of change in IRR 2010–11, 2011–12 and 2012–13



See glossary for definitions of factor used in this figure

Source: Deloitte LLP and Thomson Reuters research

Dynamic returns in 2012-13 mirrored those of 2010-11

The time periods 2010-11 and 2012-13 exhibited similar dynamic trends:

- more value was transferred to the commercial portfolio than was brought into the late stage pipeline
- an increase in the amount of time and investment incurred in late stage pipeline development exerted a negative impact on dynamic returns, and this was particularly pronounced in 2012-13
- the 2011 and 2013 yearly IRRs exhibited a significant decline from the previous year, at -2.8 and -2.4 percentage points respectively.

In contrast, for the period 2011 to 2012:

- the significant uplift from new compounds more than compensated for the value transferred to the commercial portfolio
- changes in R&D phasing (the amount of time assets spend in each phase of development) had a small, positive impact on performance returns.

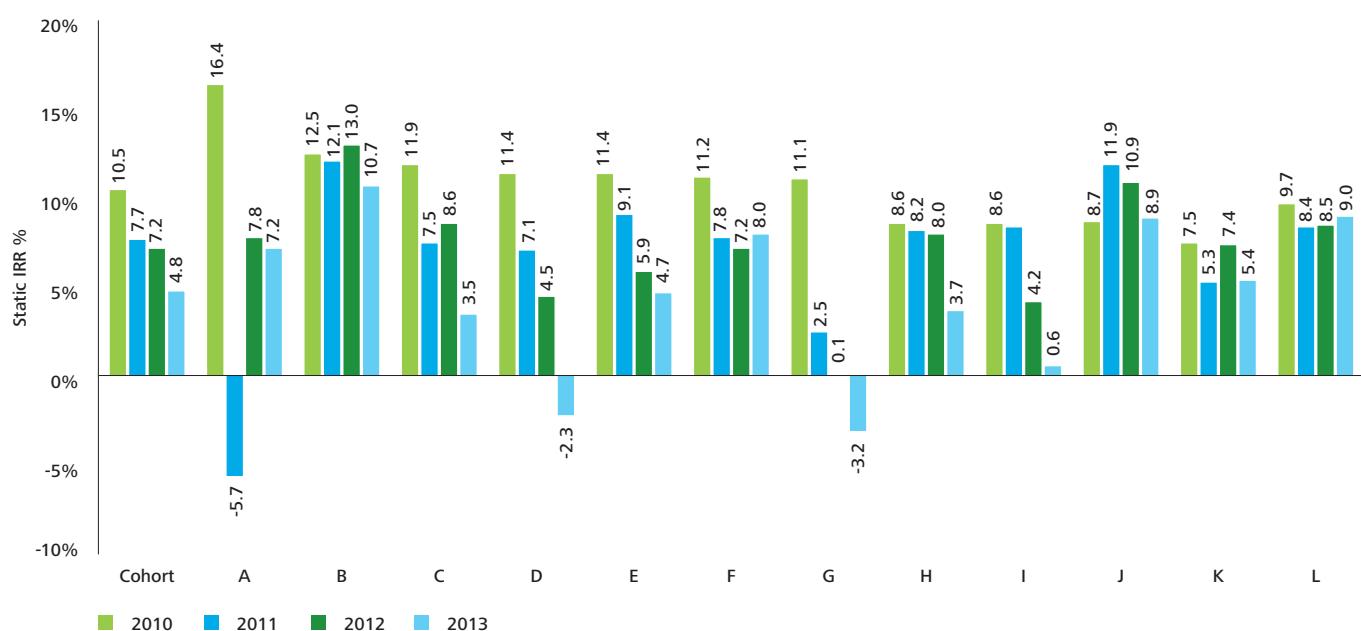
Static snapshot

The static or yearly returns measure is a snapshot in time and represents the projected returns as at 1 January for each relevant year (2010, 2011, 2012 or 2013). The modelling suggests that the average static return across the cohort declined year-on-year from 10.5 per cent in 2010 to 4.8 per cent in 2013 (Figure 3). That equates to a reduction of 54 per cent across the four years. It should be recognised that the strong projected returns in 2010 make this a challenging performance baseline for the industry.

In line with previous years, there was wide variation in performance at individual company level in 2013, with half the cohort achieving a static return above five per cent. Only one company (J) saw an improvement in the annual snapshot measure from 2010.

Over the four year period, the return across the cohort declined year-on-year from 10.5 per cent to 4.8 per cent but with wide variation, in 2013 five of the 12 companies achieved a return above 7.0 per cent.

Figure 3. Comparison of static IRR results, 2010–13



Companies labelled A to L consistent with prior reports
Source: Deloitte LLP and Thomson Reuters research

Over the four year time frame the cohort has launched 105 products with a projected value of \$770 billion and progressed 167 assets into late stage development with a projected risk-adjusted value of \$819 billion.

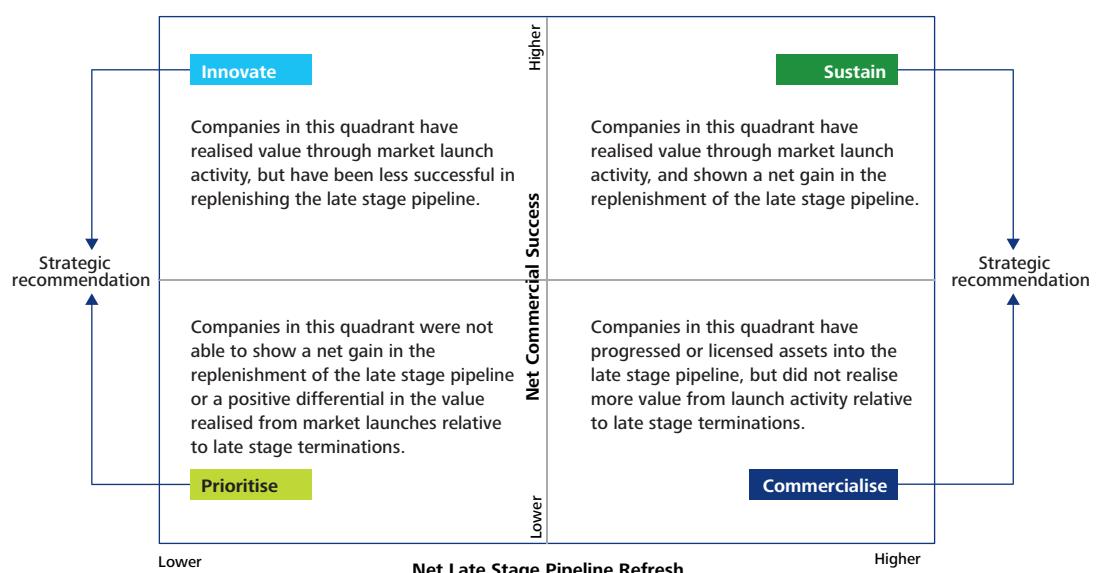
Pipeline momentum

Pipeline momentum analysis benchmarks the 12 companies, and the cohort as a whole, according to commercial success and late stage pipeline refresh:

- net commercial success is determined by assessing the impact of cash inflows associated with products that are successfully approved, offset against value lost due to terminations and stalled compounds
- net late stage pipeline refresh is the sum of changes to the forecast cash inflows for existing compounds, plus increases due to new compounds entering the late stage pipeline.

Companies in Figure 4 that successfully balanced net commercial success (high quality product approvals with few terminations) with a strong momentum into late stage pipeline (containing quality compounds with high commercial potential, few stalled compounds and high incremental revenues from new compounds) are located in the upper right quadrant (target quadrant). Those companies leading the way and proving most successful in terms of pipeline momentum are positioned at the top and to the far right.

Figure 4. Analysis of the factors underpinning year-on-year movements in returns provides further insights into company performance



Source: Deloitte LLP research

Companies are converging in terms of 2010-13 pipeline momentum

The four-year cumulative pipeline momentum view (Figure 5) shows a convergence of the 12 companies in the cohort into the target quadrant of the matrix (upper right hand quadrant). That indicates over the four-year time frame that, the majority of companies managed to balance late stage pipeline refresh with successful commercialisation.

One company (G), although successful in commercialising, struggled to pull sufficient value through its late stage pipeline. Two companies (E and J), while successfully replenishing their pipelines, were less successful in achieving commercial success.

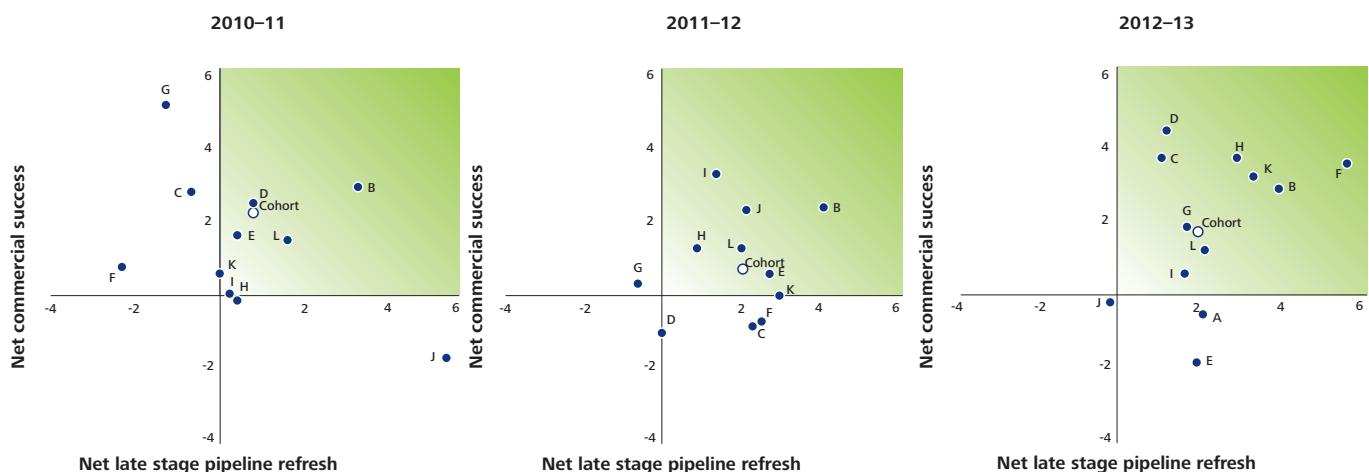
Pipeline momentum 2010-13

Pipeline momentum performance differed across the cohort in 2012-13

Comparing the pipeline momentum matrices for 2010-2011, 2011-2012 and 2012-2013 indicates that 2012-2013 was a period in which company performance diverged across the cohort (Figure 6). On average the cohort improved in terms of net commercial success and maintained its position in terms of net pipeline refresh.

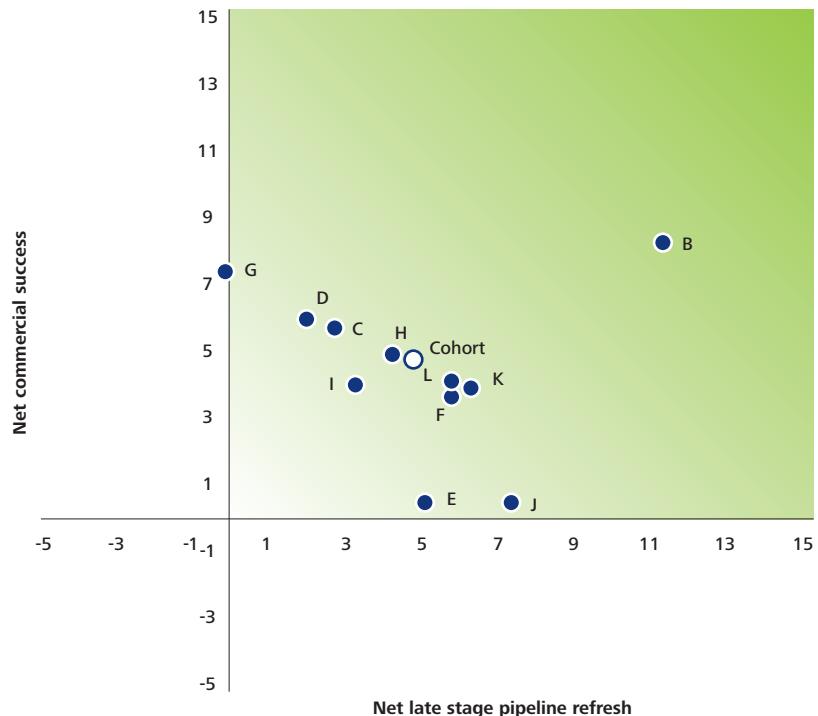
Of the 12 companies in the cohort seven exhibited an increase in commercial success in 2012-2013 compared with 2011-2012. Seven companies also exhibited an increase in late stage pipeline refresh. Five companies registered an improvement in both elements and three companies recorded a decline in both elements.

Figure 6. Pipeline momentum 2010-11, 2011-12, 2012-13



Company A only shown on 2012-13
Source: Deloitte LLP and Thomson Reuters research

Figure 5. Pipeline momentum 2010-13



Company A not shown as it sits off the scale in the upper right hand quadrant
Source: Deloitte LLP and Thomson Reuters research

Factors behind changes in pipeline momentum

Three parameters were used to assess changes in pipeline momentum over time. These were trends in the number of approvals, terminations and new compounds.

Product approvals

The number of product approvals fluctuated over time from 32 in 2010-11 to 39 in 2011-12 to 34 in 2012-13. Their total value was \$308 billion, \$196 billion and \$266 billion respectively. The average total inflow of each approval also varied over time, declining from \$9.6 billion in 2010-11 to \$5.0 billion in 2011-12, and increasing to \$7.8 billion in 2012-13.

Terminations

Comparing the three time periods the number and value of terminations remained static at approximately 20 assets and \$80 billion per year.

New compounds

The number and total value of new compounds entering the late stage pipeline fluctuated over time. The average value of new assets declined from \$5.7 billion in 2010-11 to \$4.8 billion in 2011-12. Encouragingly, this decline in average value then slowed and for 2012-13 was forecast to be \$4.6 billion per asset.

The period 2010-11 was successful in terms of commercialisation, with approvals delivering \$115 billion more value to the commercial portfolio than new compounds were able to bring to the late stage pipeline. By contrast, 2011-12 was a period of successful pipeline replenishment; there was a downturn in approvals but an upturn in new compounds entering the pipeline. The period 2012-13 was a year of equilibrium; the transfer of value to the commercial portfolio (approvals) was almost offset by the value gained from new compounds entering the late stage pipeline.

Overall late stage pipeline trends

Average cash outflow per asset increased

Between 2010 and 2013, average outflows (linked to the R&D outlay to bring a compound from discovery to late stage development) increased, while average inflows (linked to forecast revenues) declined (Figure 7). The cohort average outflow per asset in 2013 was \$923 million (this figure is not risk adjusted for late stage success rates) representing an increase of 28 per cent, or \$200 million, since 2010.

Only one of the 12 companies (L) recorded a reduction in average outflow per asset between 2012 and 2013 and the variation in average outflow per asset between companies remained wide, ranging from \$291 million to \$2,045 million.

Figure 7. Average outflow and inflow per late stage pipeline asset, 2010–2013



Source: Deloitte LLP and Thomson Reuters research

Average cash inflow per asset has declined

The cohort average inflow per asset in 2013 was \$1,927 million. This represents a decrease of 24 per cent, or \$604 million, since 2010.

Five companies recorded an increase in inflows per asset between 2012 and 2013. Again, the cohort average masks a wide variation between companies, and inflows per asset in 2013 ranged from \$962 million to \$4,000 million.

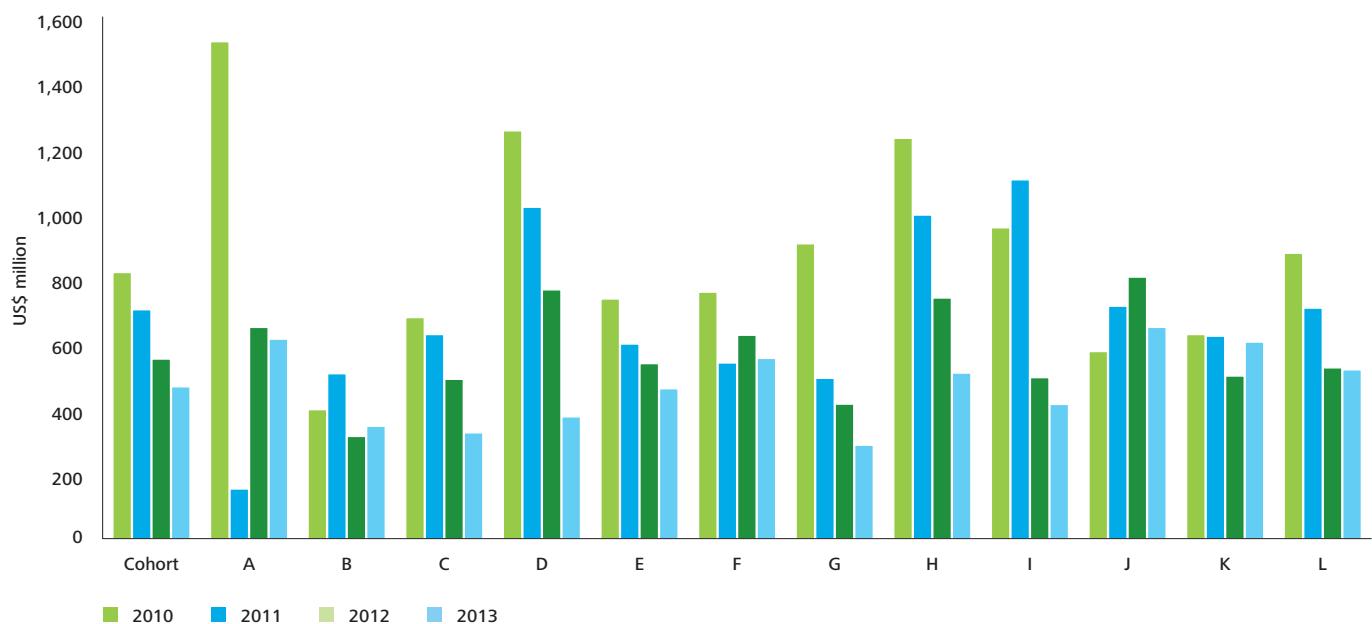
Inflows typically average two to three times the outflows required to bring the average asset to late stage pipeline. A change in inflow therefore has a higher impact on returns performance than a comparable change in outflow. Maximising inflows per asset delivers a significant uplift in returns.

Average forecast peak sales per asset have declined significantly

Average forecast peak sales for a late stage asset declined by 43 per cent between 2010 and 2013 (Figure 8). That amounted to a \$350 million reduction in average forecast peak sales for each asset from \$816 million in 2010 to \$466 million in 2013. Only one company (J) within the cohort increased average forecast peak sales per asset between 2010 and 2013 and seven of the 12 companies recorded a reduction of 40 per cent or more.

For the period between 2012 and 2013, only two companies (B and K) increased average forecast peak sales per asset.

Figure 8. Average forecast peak sales per late stage pipeline asset, 2010–2013



Source: Deloitte LLP and Thomson Reuters research

Average forecast peak sales for a late stage asset declined by 43 per cent between 2010 and 2013. That amounted to a \$350 million reduction in average forecast peak sales for each asset from \$816 million in 2010 to \$466 million in 2013.

The cost of developing an asset has increased by almost 18 per cent from 2010 to 2013

For the cohort of 12 companies, the average cost of developing an asset increased by almost 18 per cent, from \$1,094 million in 2010, to \$1,290 million in 2013 (Table 1). There was wide variation between the 12 companies, but over four years only two companies (B and L) recorded a reduction in this metric.

Average cost per asset takes into account the cost of failure of assets which do not successfully progress to Phase III development.

Table 1. Average R&D cost to develop a compound from discovery to launch, 2010–13

Company	Average cost per asset 2010	Average cost per asset 2011	Average cost per asset 2012	Average cost per asset 2013	Change in average cost per asset 2010–2013
Cohort	1,094	1,248	1,137	1,290	17.9%
A	1,803	3,229	1,657	1,893	5.0%
B	481	470	315	393	-18.4%
C	844	1,151	822	1,022	21.1%
D	1,792	2,075	2,822	3,080	71.9%
E	765	833	1,035	1,138	48.8%
F	886	1,026	1,065	1,059	19.6%
G	1,044	1,572	1,864	2,113	102.3%
H	1,887	2,011	1,651	2,136	13.2%
I	1,206	1,328	1,279	1,613	33.8%
J	1,045	853	1,105	1,133	8.4%
K	1,357	1,787	1,304	1,767	30.2%
L	1,043	1,041	712	635	-39.2%

Source: Deloitte LLP and Thomson Reuters research

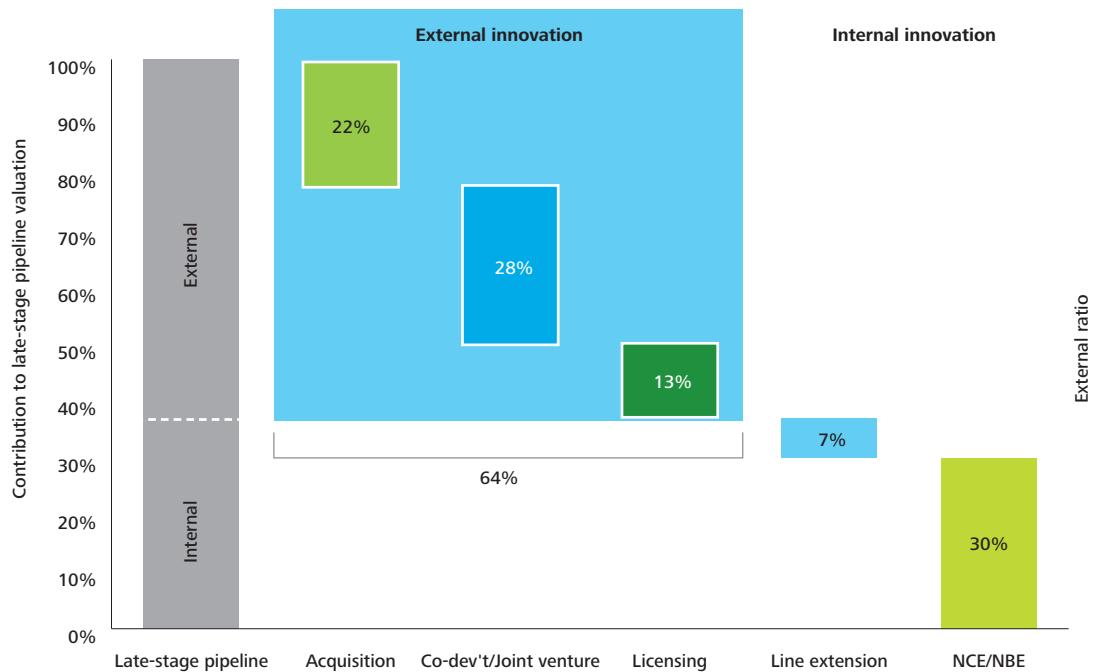
The average cost of developing an asset increased by almost 18 per cent, from \$1,094 million in 2010, to \$1,290 million in 2013.

Over 60 per cent of late stage pipeline value is generated externally

The analysis also reviewed the contribution of external science and innovation to the late stage pipelines of the cohort, to understand the productivity of early stage investments when measured by the peak sales of the assets (Figures 9 and 10). For the years 2010–13:

- 64 per cent of late stage pipeline valuation was driven by externally generated assets, for example via acquisition, co-development/joint-venture or licensing
- excluding line extensions, internal innovation (comprising new chemical entities (NCEs) and new biological entities (NBEs)) accounted for 30 per cent of late stage pipeline valuation.

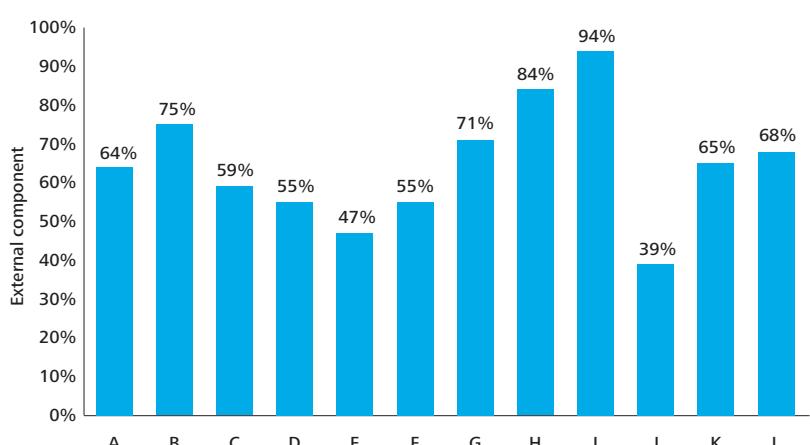
Figure 9. Source of late stage pipeline valuation, 2010–13



Source: Deloitte Consulting LLP and Thomson Reuters research
2010 to 2013 risk-adjusted peak sales projections of company late-stage pipelines
Figures are rounded to two significant figures

Ten of the 12 companies in the cohort had late stage pipeline valuations that were predominantly externally-driven (Figure 10). Two companies (E and J) have less than 50 per cent of their late stage pipeline valuation sourced externally. This external contribution was stable in recent years suggesting that investing in key capabilities to support finding, sourcing and executing agreements with external collaborators as part of the R&D organisation will be critical to the success of large pharmaceutical companies.

Figure 10. External component of late-stage pipeline valuations, 2010–13



Source: Deloitte Consulting LLP and Thomson Reuters research
Excludes line extensions and reflects NCEs and NBEs only

Insights from our year-on-year returns analysis

The analysis of year-on-year returns again highlights mixed performance at both the company and cohort level, but the four year cumulative analysis provides a more robust view of longer-term performance, with year-on-year volatility reduced.

The positive indications that suggest R&D is earning its investment:

- Over the four year time period 2010-13:
 - the number of assets in the late stage pipeline remained stable indicating that companies continued to pull through a steady number of new assets
 - the value contribution due to new compounds entering the late stage pipeline was sufficient to balance value transferred into the commercial portfolio
 - all of the 12 companies analysed performed well in terms of net commercial success, generating more value from product launches than lost from late stage terminations
 - non-R&D costs continued to decline, leading to improvements in operating margin and freeing up cash for investment in innovation
 - 11 of the 12 companies performed well in terms of net pipeline refresh, effectively replenishing their late stage pipelines
 - all but one of the cohort sat within the upper right performance quadrant of the pipeline momentum matrix, indicating that for 11 of the 12 companies improvement in performance was directionally correct, though the magnitude of the improvement needs to be scaled up.
- For the period 2012-13:
 - the average forecast value of each approval increased by 55 per cent compared with the previous year, suggesting that companies commercialised higher quality assets in this period
 - the average value of new assets stabilised after the significant decline seen between 2011 and 2012. Indeed, adjustments to forecasts for existing compounds had less of an impact on returns in 2012-13 indicating that analyst forecasts became more realistic in the face of austerity or that late R&D leaders successfully retained asset value as they progressed through the latter stages of development
 - five of the 12 companies recorded an increase in forecast inflow per late stage pipeline asset compared with the previous year, and taking into account the previous bullet point, suggesting that their focus is on higher quality assets with greater commercial potential than the previous year
 - of the 12 companies included in the cohort, seven delivered an improvement in net commercial success and seven improved in terms of net pipeline refresh
 - nine of the 12 companies exhibited an improvement in at least one of the pipeline momentum elements; five registered an improvement in both elements, highlighting variation in company performance across the cohort.

Less positive aspects of performance that R&D leaders will need to tackle:

- Over the period 2010-13:
 - R&D returns declined steadily. While new compounds delivered enough value to balance value transferred to the commercial portfolio, the uplift was insufficient to balance value leakage from terminations, reductions in forecast value for existing compounds and increasing costs
 - despite initiatives to rein in costs, the cost of developing a pharmaceutical asset increased by 18 per cent, including the cost of failure
 - the total value of companies' late stage pipelines continued to shrink, as the number of assets remained relatively constant, but average projected inflows across the cohort declined. In addition, average forecast peak sales declined by 43 per cent, indicating that approvals in the coming years may deliver reduced revenues and apply further pressure to R&D returns
 - late stage terminations remained relatively constant in terms of number and value. The cohort lost approximately \$80 billion of forecast revenue from its late stage pipeline each year due to assets failing at the final hurdles.
- For the period 2012-13:
 - compared with 2011-12, while the number of compounds was comparable, there was a decline in total value of company late stage pipelines
 - changes in R&D phasing had a greater, negative impact on returns in 2012-13, likely due to the need for longer and more complex late stage trials and delays over decisions on whether to continue asset development.

In line with last year's report, Deloitte believes that a definitive view of life sciences R&D returns and performance requires a minimum of five years of data. However, with four years of data Deloitte sees a wide variation in company performance with some clear leaders and others lagging.

Part 2: Strategies for transforming R&D returns

This year's research underlines the imperative to relentlessly pursue improved R&D returns. The analysis highlights that over the four years since 2010, gains in the value of the late stage pipeline were more than offset by value transfer or leakage. This reveals the scale and urgency of the industry's challenge, which is to ensure that the development of medicines remains commercially and economically viable, allowing society to benefit from the therapeutic potential of scientific innovation and new medicines.

Assessment of the R&D value levers indicates that organisations can focus on a number of areas to improve returns. This will rely on transformative shifts within the industry to:

- choose assets with higher commercial and therapeutic potential
- grow asset value throughout the development pathway
- mitigate against any value dilution along the development lifecycle
- accelerate development activities
- increase efforts to develop and apply strategies for cost reduction.

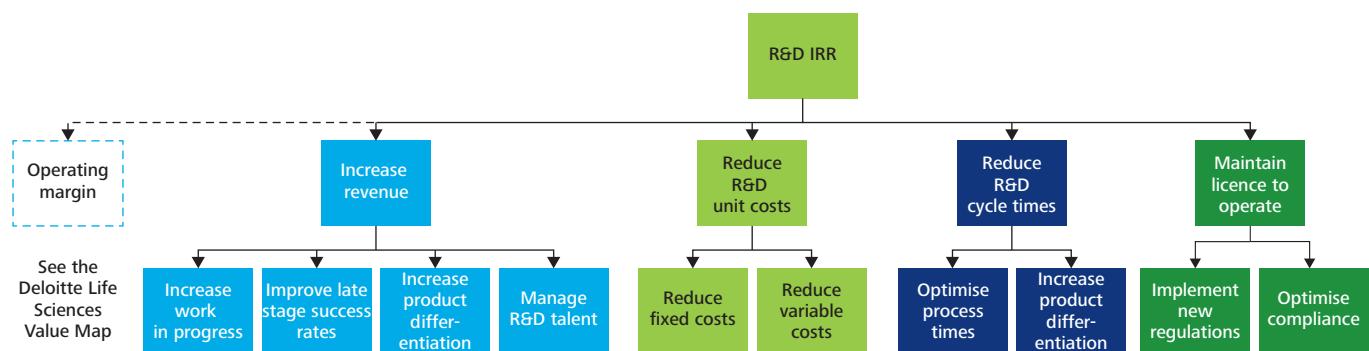
Deloitte's Enterprise Value Map for R&D (Figure 11) helps to identify areas of focus to deliver fundamental change. This section presents a summary view of actions to promote the delivery of real pipeline value to investors and society.

Deloitte's proposals this year focus on maximising the value of the science, preserving and developing talent, and enhancing capabilities in analytics; approaches that go beyond simple value preservation and straight line cost reduction to improve R&D returns.

Increase revenue

Pharmaceutical companies continue to place large bets on the basis that society will pay for their investment in innovation. Yet, this report estimates that the average commercial value of a late stage asset across the cohort has declined by 24 per cent over four years. To begin reversing this trend the industry must fulfil genuine unmet patient needs, cost effectively and with demonstrable value cases.

Figure 11. Deloitte's Enterprise Value Map for R&D (abbreviated)



Source: Deloitte LLP research

R&D in life sciences has lagged other industries in instituting analytics capabilities, to enhance decision making.

Increasing revenues is no longer the sole province of the commercial arm of a life sciences company. R&D leaders must ensure that revenue from innovation is substantial and flows mainly to the organisation irrespective of the source of the innovation (self-originated or acquired). R&D investments need to be more selective and target activities that will deliver sustainable competitive advantage, such as:

- in-house research capabilities where the organisation has, or can establish, a leadership position
- scientific risk-taking, allowing researchers to undertake activities which may have intangible value but foster innovation and maintain credibility in the wider scientific community¹
- long-range planning efforts to continually hypothesise how to exploit emerging opportunities in medical science, technology and epidemiology up to, and beyond 15 years.² This is outside the business cycle and beyond the likely tenure of today's CEOs but is critical for success in the timeframe of drug development³
- alignment of research and late stage development functions around science to create a more uniform demand pull-through from research into the larger development organisation
- engagement with academic research centres and participation in programmes, consortia and novel research initiatives with potential to unearth innovative research avenues
- improved selection of assets taken from research into the development cycle to ensure that potential products are aligned with the capability of the organisation. This will also reduce hold-ups that otherwise lead to wasted resources and value dilution
- development of combination therapies, for example in oncology and infectious diseases, that bring about a synergistic therapeutic effect by intervening at multiple points in a disease pathway
- new models of engagement and partnership with payors and reimbursers throughout the drug discovery R&D process, including during early research, to understand the value-based proposition and evidence that will be necessary to secure reimbursement. By understanding the commercial level needed for a profitable return on investment, decisions to terminate programs based on commercial factors can be undertaken earlier.

Research units are often defined as cost centres rather than revenue generating centres and can be distant from the eventual revenues accrued from launch. The difficulty in quantifying the contribution of research units to the business makes it easier to justify cost reductions in R&D. Conversely, later stage investment decisions have been harder to reject because of sunk-costs, the promise of more imminent returns and a fear of market censure where presumed future revenues are priced into the share price. This creates a difficult environment for talent management in R&D.⁴

Expanding career pathways to incorporate the rotation of R&D personnel through commercial and regulatory functions, or externally through strategic innovation or delivery partners, are two options for enhancing R&D talent management.

Competitive advantage in drug development stems from being able to understand a disease state and match the emerging clinical science of disease with novel therapeutic hypotheses. R&D in life sciences has lagged other industries in instituting modern, technologically-enabled, analytics capabilities:

- large volumes of clinical, scientific, real world and operational data generated across life sciences organisations are not fully utilised.⁵ Unlocking the full value of available data depends not only on making it accessible to business decision makers but on providing an infrastructure that allows relevant insights to be generated
- scientific evidence, when consolidated and analysed appropriately, can cut discovery time, aid hypothesis generation and maximise the value of existing assets by suggesting opportunities for compound repositioning
- analytics designed to generate evidence from real world data can help to identify unmet needs in the health system and treatment effect on outcomes, helping to build a robust case for reimbursement
- a barrier to obtaining real world evidence is the inability to access source data, in part due to concerns around use of patient information and patient privacy. A potential solution is the development of regulated good practice for the reuse of health data through consultation with stakeholders.

The key drivers for rising costs include the regulatory burden, more stringent approval requirements, sunk costs for failed compounds and more challenging disease states.

Reduce R&D unit costs

Over the four year period reviewed, R&D costs had an increasingly negative impact on dynamic returns. The key drivers for rising costs include the regulatory burden, more stringent approval requirements (especially for me-too products or compounds with marginal improvements in clinical outcomes), sunk costs for failed compounds and more challenging disease states.^{6,7}

The cost base of R&D must come down to enhance the economics of innovation. Spend must be targeted to areas that deliver competitive advantage, and companies should consider the following:

- if synthetic route design is protected through intellectual property rights (IP), synthesis can be outsourced to reduce costs. Application of this approach to appropriate research activities will directly reduce costs, retain IP and contribute to a sustainable R&D model
- identifying and embracing core external R&D capabilities. Our analysis shows that roughly 60 per cent of innovation was derived from outside of the labs of our cohort. Companies would be better served to invest and integrate capabilities such as financial structuring, scouting and deal-making to ensure that external innovation is a competitive advantage rather than an augmentation
- identify and nurture human resources in R&D that are scientifically capable but also able to integrate external services with core internal scientific capabilities.⁸ New skillsets will be needed to exploit a model that depends on the use of commoditised scientific research capabilities as widely as possible
- flatter organisational structures would allow greater flexibility and an enhanced ability to incentivise on outputs. Elimination of non-core activities implies a continued reduction of team size, and associated infrastructure. Smaller units would allow budgeting and accountability based on delivery of significant value-linked milestones
- companies should use external R&D suppliers as talent incubators, as currently seen in later phases of the lifecycle, in addition to the traditional recruitment of scientists from academia. This would ensure a continued supply of scientists trained in drug development and commercialisation even as R&D becomes leaner

- workforce analytics in R&D would allow companies to develop a granular and detailed understanding of the actual costs and capacity of their R&D organisation. This can reduce costs by identifying true core capabilities and targeting the right skills at the most valuable activities and opportunities.

Reduce R&D cycle times

R&D cycle time reduction requires action targeted at both decision making and process design. As highlighted, the choice of assets for lifecycle progression should be aligned with the development capabilities of the organisation.

For innovation sourced from outside the organisation, innovators in science routinely underestimate what is required to advance a product through the development lifecycle and tend to overvalue their IP.⁹ Externally sourced assets often require rework. To address this, R&D has a larger role to play in the art of acquisition assessment for product maturity, value and fit.

Collaboration in drug development is the next phase of converting knowledge of human biology into new medicines. As life sciences companies make efforts to work across industry, bio-incubators and academic groups, new approaches will modify the culture of the industry. They will also promote the engagement of in-house scientists, driven by the opportunities available, as well as reduce cycle time by promoting 'development-ready' investments. Some current and future trends include the following:

- large life sciences companies will make efforts to become acquirers and assemblers of scientific solutions to clinical problems. From discovery to launch, a management skillset will be required that values partnership and is able to integrate external workflows to move beyond transactional relationships
- the industry needs great scientists as development mentors to nurture innovation outside the company. Sharing drug development know-how teaches potential partners how to be successful. This scientific stewardship will allow access to more mature, differentiated products that the industry can bring into their development pipelines at the most opportune time to accelerate development
- flatter structures and stronger ties with the search and selection arms of business development functions will allow flexibility of the in-house scientific community to pursue internal and external innovation in a structured environment aligned with strategy

For the third year running, late-stage success rate is the lever by which the smallest degree of change makes the largest impact on the IRR.

- regulators are beginning to work with pharmaceutical companies to accelerate the route to market, such as products designated as breakthrough therapies by the FDA.¹⁰ This designation allows shorter, more efficient clinical trials, for example, based on surrogate endpoints
- patient recruitment remains a significant cause of delays in product development. Population analytics, similar to those used for sales forces in other industries, based on public sources of information or the wealth of clinical operational data already held by life sciences companies, will begin to allow evidence-based site and investigator selection and effective targeted recruitment efforts
- informatics combined with analytics has the potential to integrate multiple data sources to allow rapid, robust hypotheses generation for translational research planning. Examples include: de-identified cohort-discovery; managing clinical data sets, cross-trial clinical data mining, 'omics' data integration and identification of surrogate endpoints.

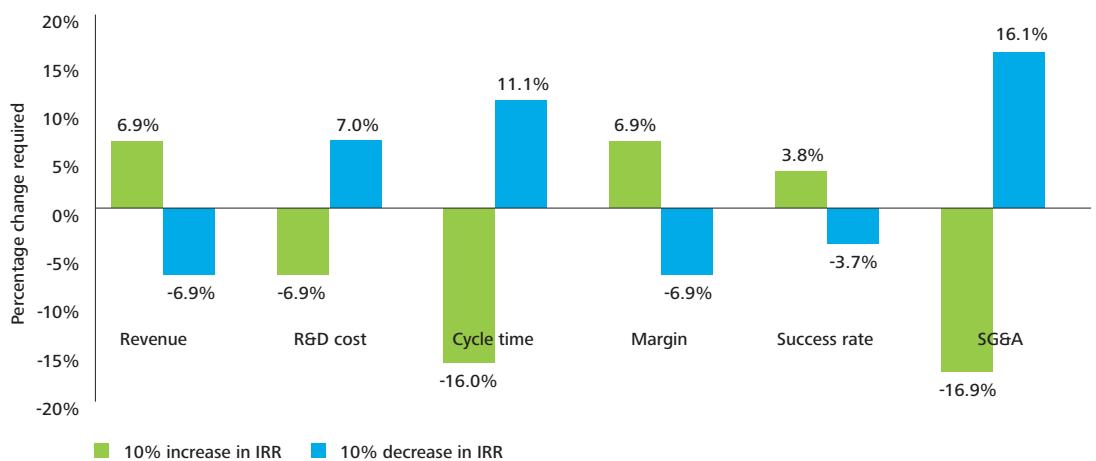
Simulating returns improvement

As in previous years, an IRR simulation assessment was undertaken for a mid-quartile company's performance, focusing on six high level R&D levers to identify the key priorities for the pharmaceutical industry (Figure 12).

For the third year running, late-stage success rate is the lever by which the smallest degree of change makes the largest impact on the IRR (a 3.8 per cent improvement in late-stage success rate would increase yearly returns by 10 per cent). The effect of improving the likelihood of regulatory approval makes a compelling case for excellence in product selection and development decision making.

Changes in revenue, net margin and R&D cost show an increased power to influence returns in line with continuing healthcare payer austerity impacting reimbursement rates and an 18 per cent increase in cost per asset.

Figure 12. Change in value levers required for an increase or decrease in yearly returns of ten per cent



Source: Deloitte LLP and Thomson Reuters research

SG&A = Costs of sales, goods and administration
See Appendix 1 for the sensitivity analysis methodology

Part 3: Conclusions

Analysis of R&D performance from 2010 to 2013 shows that projected R&D returns steadily declined. The cohort average hides a wide variation in performance, yet 11 of the 12 companies moved in the right direction in terms of replenishing their pipelines and successfully commercialising new medicines. The challenge they must address is how to accelerate pipeline momentum trajectory while driving higher cost efficiencies in their R&D operations. Unfortunately, the value derived from new compounds entering the late stage pipeline was not sufficient to offset the transfer of value into the commercial space alongside value leakage from terminations, stalled compounds, downgraded forecasts for existing pipeline assets, and margin and cost factors that exerted downward pressure on returns.

Four years does not provide sufficient data to predict future trends with confidence, but it does highlight areas in which the cohort made headway and those where attention is needed.

Positive signs for R&D performance:

- from 2010 to 2013, the cohort of 12 companies launched 105 products with a projected value of \$770 billion into the commercial portfolio and pulled through into late stage pipelines 167 compounds with a total risk adjusted value of \$819 billion
- over a four year time frame, the elements of pipeline momentum were balanced; companies are performing well in terms of both net commercial success and net late stage pipeline refresh
- the cohort appears to have focused on higher quality assets with greater commercial potential. Over the most recent time period, while the number of approvals marginally declined, the average forecast value of approvals increased by 55 per cent compared with 2012. For the same period, five of the 12 companies recorded an increase in average inflow for their late stage assets
- operating margins continued to improve due to a steady decline in non-R&D costs. That exerted a small, but positive influence on R&D returns.

Areas of concern:

- the total value of companies' late stage pipelines continued to decline. Companies struggled to increase the number of late stage assets, and moreover, the inflows these assets were forecast to deliver declined, as did average forecast peak sales
- targeting the cost of failure remains a key priority; the cohort made little, if any, progress in reducing value leakage due to late stage terminations
- although the methodology incorporates an inherent time lag and considers ten years of historical R&D cost, a positive impact from actions taken to reduce R&D costs might have been anticipated. However, the most recent period saw an increase in the average cost to develop an asset (which includes the cost of failure) and an increase in R&D phasing, and both had a greater negative impact on R&D returns than in previous years.

This year's findings confirm that life science R&D returns remain challenging, but there are signs that the leaders in the cohort are weathering the storm.

This year's findings confirm that life science R&D returns remain challenging, but there are signs that the leaders in the cohort are weathering the storm.

Appendix 1: Methodology

Deloitte LLP in association with Thomson Reuters has built an interactive model to calculate the Internal Rate of Return (IRR) for the companies and compounds of interest. This section describes which companies and compounds are included, and details the methodology, model inputs, outputs and assumptions used to generate individual and cross-company IRR metrics.

Company cohort

The analysis focuses on the same 12 companies that were included in our previous reports (published in 2010, 2011 and 2012); namely the top 12 publicly-listed research-based pharmaceutical and biotechnology companies measured by 2008-2009 R&D spend. These companies comprise: Amgen, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck & Co., Novartis, Pfizer, Roche, Sanofi and Takeda. The cohort is consistent for 2010, 2011, 2012 and 2013.

Compounds evaluated

The IRR analysis focuses on each company's late stage pipeline defined as the set of compounds that are either in phase III development or submitted for approval as of 30th April for each relevant year (2010, 2011, 2012 and 2013). The types of compound included in the late stage pipeline comprise:

- new chemical entities (NCEs)
- new biological entities (NBEs)
- significant line extensions – those expected to result in a measurable uplift in revenues
- reformulations
- biosimilars.

For all compounds included in the late stage pipeline, their origin was assessed and they have been categorised as:

- self-originated
- in-licensed – acquired through a licensing agreement with a third party
- joint venture – actively being developed as part of a partnership agreement with one or more third parties
- acquired as part of a business combination, either a merger of two corporations or acquisition of one corporation by another.

Methodology – Principles applied to the model

Currency

All calculations have been performed in US dollars. Where historic source data has been presented in currencies other than US dollars, it has been converted using the Financial Times yearly average rate for the relevant year. Where forward looking data is in currencies other than US dollars, the current Financial Times prevailing 12 month average rate has been used for conversion into US dollars.

Taxation

IRR has been calculated based on post tax inflows and outflows. Company specific tax rates have been calculated based on average effective tax rates over the 10 years to 31 December 2010, 2011, 2012 or 2013, adjusted for non-recurring items, such as litigation costs, impairments and in-process R&D expense.

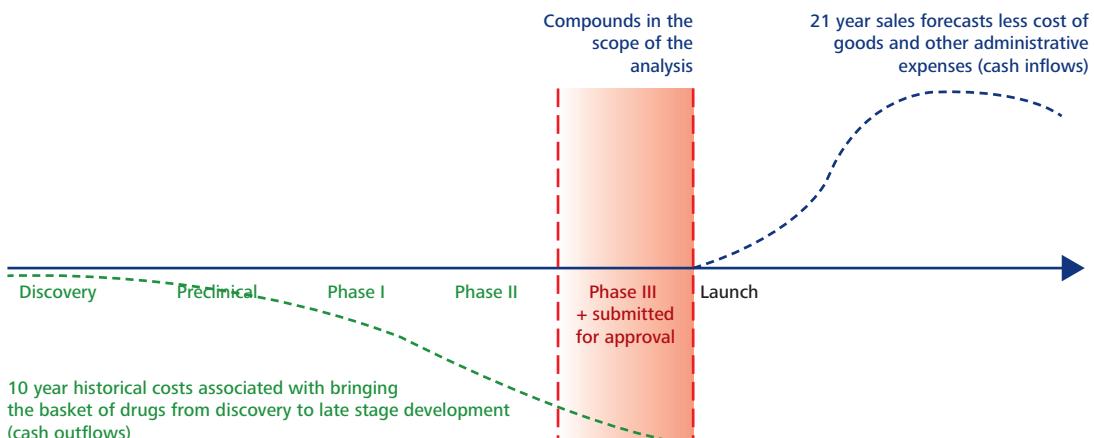
IRR calculation

IRR is a measure which equates the cost of developing an investment and the expected benefits that the investment will deliver. The methodology assesses two IRR measures; yearly, snapshot returns performance and dynamic, year-on-year returns performance.

Static IRR

Figure 13 summarises the methodology used to calculate forecast performance returns and estimated costs. It equates cash outflows with cash inflows to generate an IRR value, with a separate IRR value generated for each of the four years under investigation, 2010, 2011, 2012 and 2013.

Figure 13. Calculating yearly, static IRR



Source: Deloitte LLP

Yearly, static IRR is calculated for a defined basket of last stage compounds by estimating the expenses associated with developing the compounds and the likely potential returns that they will deliver. This is achieved using estimates of each company's:

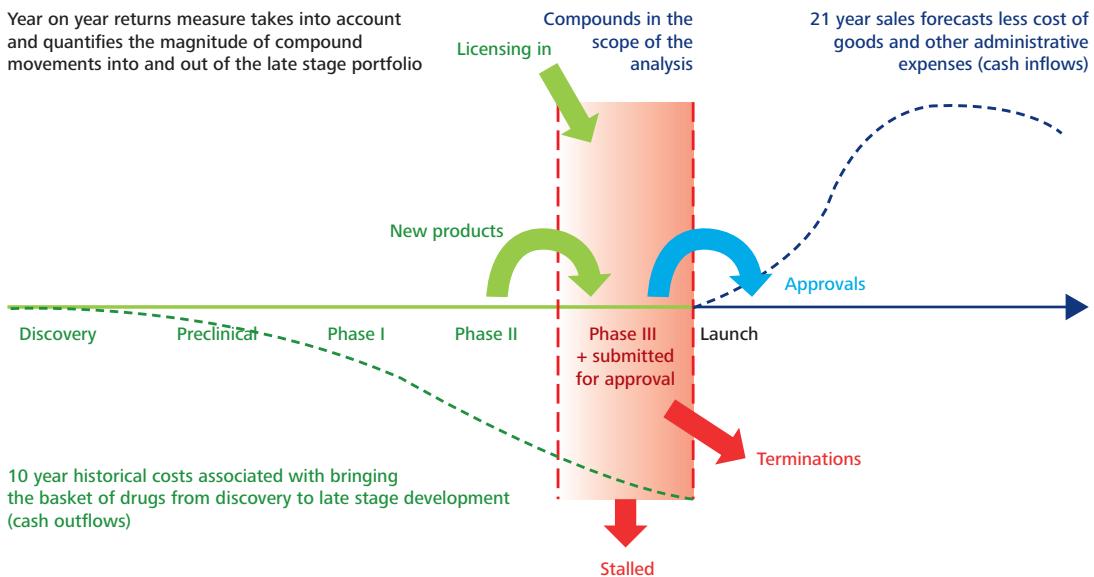
- Annual R&D expenses (cash outflows) for the prior 10 years – which calculates the cost associated with bringing the basket of compounds to a particular stage of development

- Annual risk adjusted revenues (cash inflows) forecast for the future 21 years – which estimate the likely returns that the basket of compounds will deliver.

Dynamic (year-on-year) returns performance

The methodology used to determine the drivers of year-on-year changes in returns performance is summarised in Figure 14.

Figure 14. Determining the drivers of year-on-year dynamic returns



Source: Deloitte LLP

Calculating the dynamic returns performance allows the movement in static, snapshot returns performance from one year to the next to be reconciled and also quantifies the key elements driving this change. It is calculated for three time periods; 2010-11, 2011-12 and 2012-13. Dynamic returns performance focuses on the same baskets of late stage pipeline compounds as yearly, snapshot returns performance, however, the basket of compounds changes year-on-year due to movement of compounds into and out of the late stage pipeline.

The elements driving change in IRR can be categorised into two groups, based on whether they impact cash outflows or cash inflows.

Cash outflow elements

The four outflow elements driving change in IRR comprise:

- R&D cost – changes to R&D costs for self-originated compounds
- cost phasing – changes to how R&D costs are allocated over the historical 10 year time period
- licensing – increases or decreases in licensing expenses associated with the basket of compounds under review
- tax rates – alterations to the company specific tax rates based on average effective tax rates over the historical 10 year period.

The annual impact of each factor on the cash outflows has been inputted into the models in isolation so that their individual impact on the IRR can be quantified, given constant inflows.

Cash inflow elements

The six inflow elements driving change in year-on-year returns performance comprise:

- terminated – future revenues lost from late stage pipeline due to termination of compounds through either company or regulatory termination
- approved – transfer of revenues to the commercial portfolio due to compounds leaving late stage pipeline and being launched
- existing – increases or decreases in forecast revenues for compounds which remain within the late stage pipeline
- new – revenues associated with new compounds entering the late stage pipeline
- stalled – revenues lost due to compounds which are not officially terminated but which are unlikely to launch, for instance due to the publication of negative clinical trial data
- margin – changes in a company's average cash operating margin.

The annual impact of each factor on the cash inflow has been inputted into the models in isolation so that their individual impact on the IRR can be quantified, given constant outflows.

Model inputs: R&D cash outflows

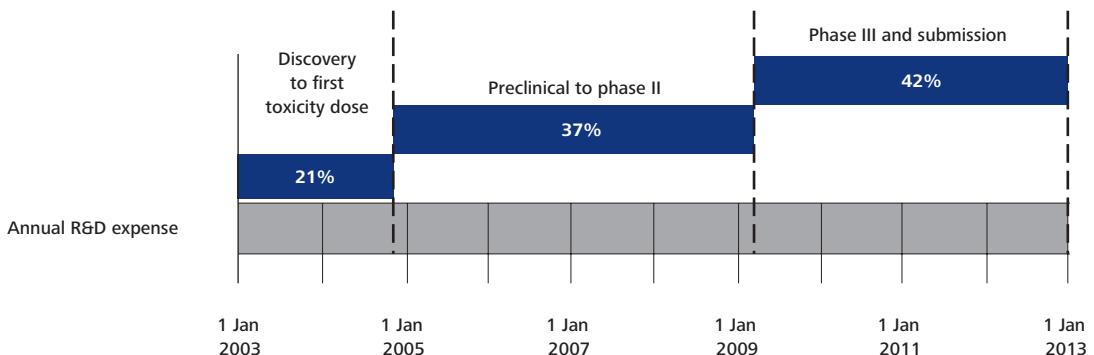
For all compounds included within company late stage pipelines, the origin of the compound was assessed. Compounds were categorised as; self-originated, acquired through in-licensing, or acquired through a business combination.

Self-originated compounds

1. R&D costs have been obtained from publicly available company reports results based on applicable GAAP at the time results were issued (either local GAAP applicable in the country of incorporation, IFRS or US GAAP).
2. R&D costs recognised through profit and loss accounts are assumed to equal cash flows, unless a non-cash expense is separately disclosed (e.g. an inprocess R&D charge recorded under US GAAP) in which case this has been excluded from the R&D cost.
3. Following a business combination, R&D costs include those of the enlarged group, in line with the publicly available company reports (see below for pre-acquisition costs).

4. The use of publicly available data limited the model to the use of industry average cycle times and cost allocation when calculating R&D costs over the ten year period. Benchmark data (Source: CMR International 2013 Pharmaceutical R&D Factbook) was used to allocate costs as shown in Figure 15. Compared with last year, industry average cycle times remained relatively unchanged; preclinical to Phase II remained unchanged at 5.1 years, and Phase III to launch increased from 3.4 to 3.9 years. Cost allocation has changed as shown in Table 2. This methodology incorporates the cost of attrition of assets from the initial cohort at discovery to the late stage pipeline as at 1 January 2010, 2011, 2012 or 2013.
5. R&D costs have not been included within the model beyond 31 December 2012.

Figure 15. Allocation of R&D costs and cycle times, 2013



Source: CMR International 2013 Pharmaceutical R&D Factbook

Table 2. Change in R&D cost allocation: 2010, 2011, 2012 and 2013

R&D phase	2010 report	2011 report	2012 report	2013 report
Discovery to first toxicity dose	25%	25%	28%	21%
Preclinical to Phase II	20%	29%	33%	37%
Phase III and submission	55%	46%	39%	42%

Source: CMR International 2013 Pharmaceutical R&D Factbook

Compounds acquired through in-licensing

1. Where a compound included within the company late stage product portfolios has been in-licensed from a third party, any upfront payments have been included in the relevant year of acquisition.
2. In-licensing information was obtained from publicly available sources through proprietary secondary desk research conducted by Deloitte LLP. In most cases financial information was limited due to the commercial sensitivity of deal information.
3. As publicly available data typically does not include the timing or quantum of future contingent payments, the total amount of these costs associated with the relevant in-licensed compound have been assumed to be incurred at their maximum potential amounts on commencement of sales of the compound.
4. Any costs expended in developing the product subsequent to the in-licensing have been included as per the internally developed compounds.

Compounds acquired as part of a business combination

1. R&D costs arising from compounds acquired as part of a business combination enacted by an entity have been included in the model if considered material to the calculation of IRR.
 - a. R&D costs incurred after the date of the business combination have been included as per the internally developed compounds noted above.
 - b. R&D costs incurred prior to the date of the business combination have been included separately in the model obtained from publicly available company reports results based on applicable GAAP at the time results were issued (either local GAAP applicable in the country of incorporation, IFRS or US GAAP).
2. Private companies acquired were not considered as access to the required financial data is not widely available.

3. The cost associated with the acquisition of a compound as part of a business combination has not been included as the acquired company's pre-acquisition R&D cost is included as per the internally developed compounds. Furthermore publicly available data does not typically include the fair value attributed to each of the compounds acquired.

4. Any costs expended in developing the product subsequent to the business combination have been included as per the internally developed compounds.

Model inputs: Forecast cash inflows

Revenue forecasts

1. Company revenues were forecast for a 21 year time frame for each time period under investigation as follows:
 - a. 2010 models – revenues forecast from 1 January 2010 – 31 December 2030
 - b. 2011 models – revenues forecast from 1 January 2011 – 31 December 2031
 - c. 2012 models – revenues forecast from 1 January 2012 – 31 December 2032
 - d. 2013 models – revenues forecast from 1 January 2013 – 31 December 2033.
2. Revenue forecasts were calculated by Thomson Reuters using consensus forecasts extracted from Thomson Reuters' Cortellis and proprietary modelling techniques to generate revenues to 2033.
3. Revenue forecasts have been risk adjusted for phase III and submission success rates, specific to therapeutic areas (CMR International Global R&D metrics programme 1994-2011). The risk of a product being withdrawn once it has come to the market has not been assessed in this model. The risk of product withdrawal compared with the potential risk of failure during development is relatively small. Also the probability of post-launch withdrawal is highly variable dependent on a number of factors and is therefore difficult to model accurately.

4. Revenue streams were forecast using Thomson Reuters' 2013-2017 consensus forecast data, combined with a proprietary sales forecast model. This model used consensus forecast data as a basis in tandem with a weighted average growth of the previous three years of sales data and a factor to indicate the saturation of the market, to calculate the desired year's sales data. Sales uptake curves were modelled using this methodology combined with an assessment of a compound's individual characteristics (e.g. molecule type, indication, mechanism of action and target) to understand if a compound had high, medium or low sales potential. Forecasts were validated using external data sources to check drug peak sales potential and overall market sizes and principles.

5. Consensus sales data was obtained in August 2013; therefore forecasted revenues are accurate as of this date.

6. After peak sales had been reached, standard erosion curves were applied dependent on the molecule type (e.g. small molecule or biologic); different erosion curves have been used for small molecules (chemical entities) and large molecules (biological entities). The use of different erosion curves reflects the stringent competition in the small molecules generic market where, in extreme cases, loss of sales can happen in a matter of weeks and months. On the other hand the arrival of biosimilars into the generics market is likely to have a less profound effect around loss of sales for biologics.

7. Small molecule and biologic curves are as follows (please refer to Figure 16):

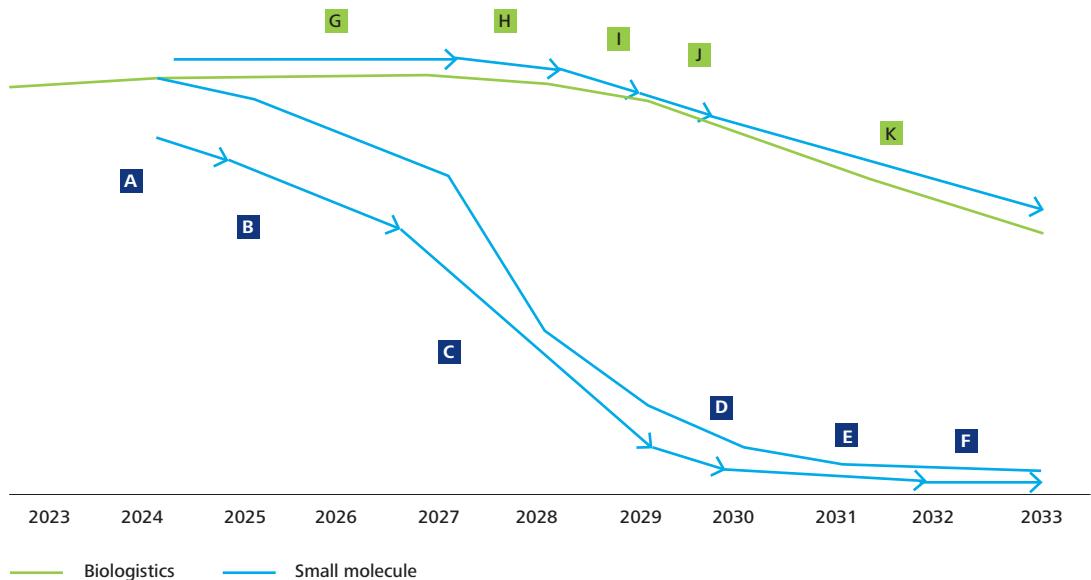
For small molecules

- a. A five per cent decrease in sales two-three years prior to patent expiration
- b. A ten per cent year on year decrease in sales for two years prior to patent expiration
- c. Once patent expiration occurred a 50 per cent year on year decrease in sales for four years
- d. A 25 per cent decrease in sales for one year
- e. A ten per cent decrease in sales for two years
- f. A five per cent decrease in sales from thereafter until 2033.

For biologics

- g. No decrease in sales to patent expiration
 - h. A two per cent decrease in sales for one year
 - i. A five per cent decrease in sales for two years
 - j. A nine per cent decrease in sales for one year
 - k. A ten per cent decrease in sales until 2033.
8. The anticipated introduction of biosimilars over the short and medium term is likely to be slow. This is due to a number of factors including the number of biologics on the market compared with small molecules and the need to prove bioequivalency for biosimilars. It is therefore assumed that erosion of biologics sales will be considerably smaller compared with that of small molecules.
9. Available patent information was extracted by Thomson Reuters from Thomson Reuters Cortellis or Newport for Generics for each compound. A patent landscape for an individual compound can be extremely complex involving upwards of 20 patents varying in nature and geographic application. To define patent expiration the following rules were applied to intellectual property records:
- a. The Newport Constraint Date (NCD) was given precedence based on patents for major markets (USA, Europe and Japan). This date is the expected date of generic entry based on the opinions of Newport analysts.
 - b. Newport patent dates were also consulted: all patents relating to a compound were considered when defining patent expiry.
 - c. Product patents were used as the primary source for definition of a patent expiry date.
 - d. Where product patent information was inconclusive secondary patents were used to define patent dates.
 - e. For reformulations and line extensions other patent types were used to understand where five year patent extensions were appropriate.

Figure 16. Diagrammatic representation of small molecule and biologic sales erosion curves



Source: Thomson Reuters

Margin applied to forecast revenues

Inflows have been determined by applying an average cash operating margin to revenues over the forecast period.

1. The average cash operating margin has been calculated using reported operating profit over the ten years preceding each year, 2010, 2011, 2012 or 2013, adding back R&D expense and depreciation/amortisation, and deducting capital expenditure and non-recurring costs. No adjustment has been made for working capital.
2. Reported operating profits have been obtained from publicly available company reports based on applicable GAAP at the time results were issued (either local GAAP applicable in the country of incorporation, IFRS or US GAAP).

3. Depreciation and amortisation includes directly related impairment charges.
4. Non-recurring costs include litigation costs, profits or losses arising from the sale of businesses or fixed assets, restructuring costs and profits or losses from equity investments.
5. Where operating profits include finance costs, these have been excluded from the calculation.
6. Average cash operating profits over the ten year period used to estimate cash outflows are assumed to equate to future margins over the 21 year revenue forecast period.

Sensitivity analysis

Sensitivity analysis was conducted across six high level R&D value levers to realise a ten per cent change in IRR.

- *Revenue:* to effect the revenue changes, inflow was increased or decreased by the same proportion each year, over the 21 year forecast revenue period.
- *Cost:* to effect the cost changes, outflow was increased or decreased by the same proportion each year over the ten year period.
- *Cycle times:* the effects of cycle time changes were calculated by altering the launch dates of the portfolio of assets and spreading the resultant costs and revenues over the altered periods. Thus the IRR is affected by both the change in forecast revenues and an alteration in the discounting profile.
 - For decreased cycle times, overall costs were not changed, however the period over which they were incurred was shortened. Total revenues are increased to take into account the earlier launch dates of the portfolio of assets, by increasing the number of years of peak revenue.
 - For increased cycle times, overall costs were not changed; however, the period over which they were incurred was increased. Peak revenues were decreased to take into account the later launch dates of the portfolio of assets.
- *Success rates:* sensitivity to success rates is analysed by varying late stage success rates by a constant factor across all products to effect the desired ten per cent increase or decrease in IRR.

Modelling assumptions

The use of revenue forecast data and publicly available information regarding pipelines and deal information presents certain challenges and risks associated with the construction of revenue forecasts and distribution of R&D costs within the life sciences industry. These challenges and risks include, but are not limited to, the following:

1. The late-stage pipeline is an accurate reflection of the pipeline, as of April 2010, 2011, 2012 or 2013. This incorporates all public information available at that date. There is often a lag in obtaining intelligence on product launches, particularly of line extension products, and intelligence on new Phase III compounds entering the late-stage pipeline. This may mean products are removed from the pipeline the year following launch or may have a delay in pipeline inclusion until the year following Phase III entry.
2. Deal and licensing information is commercially sensitive and therefore exact financial information is limited. During the research phase several proprietary databases and publicly available information have been used to construct an accurate picture of the costs associated with compounds. It is important to note however that not all in-licensing and deal financial information is available outside of the companies involved, therefore some deal information used within this study does not have financial values associated with it.
3. The revenue and portfolio information provided in this report constitute forward looking statements relating to the financial, operational and performance of specific companies. Although the authors of this report believe these forward looking statement are based on reasonable assumptions listed here, any forward-looking statements by their very nature, involve risks and uncertainties. These forward-looking statements may be influenced by factors which affect actual outcomes or results to be materially different from those predicted here.
4. All forward-looking statements reflect knowledge and information available as of August 2013 and may not be updated post publication.
5. In-licensing costs included in the model are limited to those products included in the late stage pipeline, thus in-licensing costs associated with compounds that failed prior to Phase III are not included.

6. The use of publicly available data limited the model to the use of industry average cycle times and cost allocation when calculating R&D costs over each 10 year period. This prevents an assessment of differences in development performance between each organisation, for example, therapeutic area and development programme specific cycle times are ignored and companies with better than average cycle times are not rewarded in this model.
7. Forecast R&D costs have not been included within the model beyond 31 December 2013 as accurate and relevant information is not available.
8. The assumption that average cash operating profits over the ten year historical time period equate to future margins over the 21 year revenue forecast period may fail to fully reflect the impact of recent corporate cost reduction initiatives where relevant.
9. Revenue forecasts have been risk adjusted using historical Phase III and submission success rates that may not model potential future changes in the regulatory and payer environment.
10. The model is sensitive to the distribution of compounds across the late stage pipeline (Phase III to submission) and as this drives cash flow timing, a snapshot taken in a different year could generate different results.
11. Important factors that could cause actual results to differ materially from those contained in forward-looking statements, certain of which are beyond our control, include, among other things: the loss or expiration of patents, marketing exclusivity or trademarks; the risk of substantial adverse litigation/government investigation claims and insufficient insurance coverage; exchange rate fluctuations; the risk that R&D will not yield new products that achieve commercial success; the risk that strategic alliances will be unsuccessful; the impact of competition, price controls and price reductions; taxation risks; the risk of substantial product liability claims; the impact of any failure by third parties to supply materials or services; the risk of failure to manage a crisis; the risk of delay to new product launches; the difficulties of obtaining and maintaining regulatory approvals for products; the risk of failure to observe ongoing regulatory oversight; the risk that new products do not perform as expected; the risk of environmental liabilities; the risks associated with conducting business in emerging markets; the risk of reputational damage; and the risk of product counterfeiting. Nothing in this document should be construed as a profit forecast.

Notes

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Glossary

Asset: a pharmaceutical compound that is currently in Phase III or has been filed for regulatory approval for any indication, which if successful in progressing to launch will generate future economic benefits for the company.

Average R&D cost per asset: the average cost to develop a compound from discovery to commercialisation. Calculated by risk-adjusting the average expenses (outflow) per asset by phase III and submission success rates.

Cohort: the top 12 research-based pharmaceutical and biotechnology companies, measured by R&D spend in the 2008/09 financial year.

Commercial success: level of success exhibited by each company in terms of its ability to progress compounds through late stage development to launch. Commercial success is determined by two key events; loss of compounds from the late stage pipeline due to terminations and exit of compounds from late stage pipeline due to successful product approval and launch.

Cost phasing: refers to the use of pharmaceutical industry average R&D cycle times and R&D cost allocation when calculating R&D cost over the historical 10 year period to 31 December 2010, 2011, 2012 or 2013.

Dynamic IRR: IRR calculated over a number of years (2010-2011, 2011-2012, 2012-2013 or 2010-2013) to provide analysis of IRR trends over time.

Dynamic returns: reconcile the movement between snapshot or *yearly performance returns*.

Existing compounds: Existing compounds are those that appear in a company's late stage pipeline for a given year, and remain within the late stage pipeline for the next year. The revenue forecasts associated with the compound may have changed between the time periods under review due to additional information being available on the compound and/or its indication.

Inflows: Forecast sales that each company's late stage pipeline is estimated to generate, less cost of goods sold and other administrative expenses. Determined by applying an average cash operating margin to *risk adjusted revenues* over the 21 year forecast period.

Internal rate of return (IRR): a profitability measure which equates the cost of an investment and the expected benefits that the investment will deliver. IRR is calculated on a net present value basis and is the discount rate which makes the net present value of the cash flows expected for an investment equal to zero.

Late stage pipeline: the basket of compounds for each company that are in either Phase III clinical development or submitted for approval as of April for a given year (2010, 2011, 2012 or 2013).

Late stage terminations: compounds whose development has been terminated or failed in Phase III or submission through either regulatory rejection (regulatory terminated) or as a consequence of an internal company decision (self terminated).

Licensing/in-licensing costs: costs associated with the licensing-in of compounds to the late stage pipeline. This data has been sourced from the public domain. Upfront payments are included in the relevant year of acquisition. Publicly available data typically does not include the timing and amount of future contingent payments, therefore the maximum potential amounts of these costs has been applied to the product's first year of forecast sales.

Margin: the average cash operating margin has been calculated using reported operating profit over the 10 years prior to the relevant year; 2010, 2011, 2012 or 2013. R&D expense and depreciation/amortisation have been added back, capital expenditure and non-recurring costs have been deducted. Future margins over the 21 year revenue forecast period are assumed to equate average cash operating profits over the ten year period under investigation.

Late stage pipeline refresh: the sum of increased revenue forecasts due to new products entering the *late stage pipeline* and changes to revenue forecasts for existing late stage compounds.

New compounds: New compounds are those that appear in a company's late stage pipeline for a given year, but were not part of the late stage pipeline the previous year.

Outflows: total expenses which have been invested to develop a company's basket of late stage pipeline compounds. Outflows include both R&D costs, sourced from company profit and loss accounts, and non-cash expenses which have been disclosed, for example licensing-in costs.

Pipeline momentum: one of the dimensions of *dynamic IRR* or *dynamic returns*. Pipeline momentum explains the changes in forecast revenue from one snapshot IRR to another and is a combination of *commercial success* and *late stage pipeline refresh*.

Product approvals: compounds which were included in a company's late stage pipeline in a given year, but in the following year received regulatory approval and launched in at least one major market.

Regulatory terminated compounds: compounds that were part of a company's late stage pipeline in a given year, but which are no longer included as they were rejected by regulatory authorities the following year. Future revenues derived from these compounds are not included in the static IRR calculation for subsequent years.

Risk adjusted revenues: calculated by applying a *success factor* to forecast sales revenue for each company's *late stage pipeline*. This takes into account the likelihood of compounds progressing from Phase III to submission, and submission to launch.

R&D cost: calculated using company R&D expenses reported in company profit and loss accounts.

Self-terminated compound: a compound that was part of a company's late stage pipeline in the 2010, 2011 or 2012 analysis, but which is no longer included due to the company's decision to terminate its development. Future revenues derived from such compounds are not included in the static IRR calculation for subsequent years.

Static IRR: IRR calculated for a given year (2010, 2011, 2012 or 2013), to provide a yearly snapshot of IRR performance. Calculated on the *late stage pipeline* as of 1 January each year, using 10 years of historical cash outflows and 21 years of forecast annual cash inflows.

Success factor: factor calculated to reflect the probability of success for each company's *late stage pipeline*. Uses a combination of Phase III and submission success rates across the *late stage pipeline*.

Tax rates: company-specific tax rates have been calculated based on average effective tax rates over the 10 years to either 31 December 2010, 2011, 2012 or 2013, adjusted for non-recurring items such as litigation costs, impairments, in-process R&D expense.

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We would like to acknowledge the significant contributions received from Mark Stockbridge and Johnathan Lowery. We would also like to thank Oliver Whight, Anthony Leese, Colin Terry, Kevin Dondarski.

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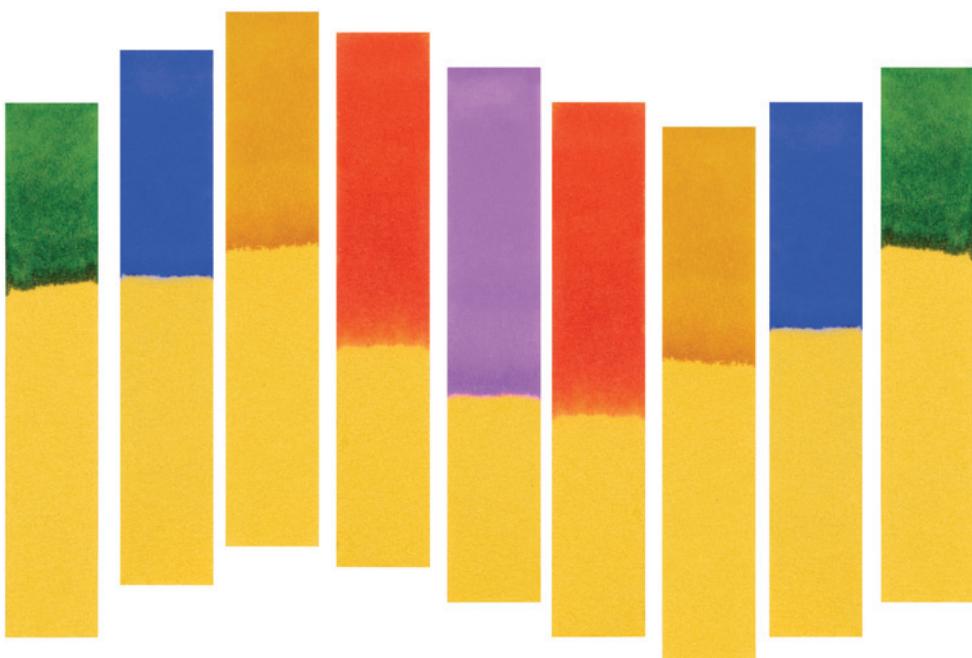
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Designed and produced by The Creative Studio at Deloitte, London. 31515A