

Measuring the return from innovation

Is R&D earning its investment?



2011: Our annual review of how the life sciences industry is performing in generating value from R&D

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Deloitte and Thomson Reuters have collaborated in this study of R&D value measurement, combining Deloitte's R&D advisory experience and financial expertise with Thomson Reuters R&D data and business insights.

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Foreword

From static to dynamic returns

Against a background of rising costs and declining output, R&D leaders in life sciences are under continued pressure to justify the investment in R&D.

Our annual review of R&D returns in life sciences aims to provide methods, insights and actionable recommendations that can help measure, understand and ultimately improve value realisation in the industry. In doing so, we intend to help R&D leaders better manage and make the case for investment in 'the business of R&D', and thereby develop more medicines that are of benefit to patients and society.

Last year, using proprietary methodology, Deloitte and Thomson Reuters conducted an assessment of R&D returns for the top 12 companies by R&D spend at the 'whole R&D business' level, rather than at the asset level, using Internal Rate of Return (IRR).

This year, we look at the performance of the same cohort of companies one year on. At the cohort level, there has been an overall decline in returns. The majority of companies have seen a decrease in IRR, bringing the cohort IRR down from 11.8% in 2010 to 8.4% in 2011. While this picture reflects the very real productivity challenges the industry is facing, it belies some underlying successes.

We introduce the concept of dynamic returns to explore the factors behind movements in our year-on year (static) IRR measure. We also outline a method to evaluate the two dimensions that make up dynamic returns: 'pipeline momentum' and 'margin and cost factors', and compare company performance on this basis.

Interpreting our findings

We believe that, in life sciences, dynamic R&D returns should be looked at over a four to five year minimum timeframe (a representative duration for a successful product to progress through late stage development). In this context, our report sets out how the returns performance of the company cohort compares to the baseline that we published in 2010, whilst acknowledging the limitations associated both with the assumptions of our methodology, and with inappropriately extrapolating a one year movement in returns performance.

In our view R&D returns must inform but not prescribe the strategy and actions of R&D leaders and their teams in driving the business of R&D. Maintaining R&D value discipline is important in framing and quantifying the opportunity to improve innovation productivity. Against this backdrop, we suggest change opportunities where R&D leaders might seek to focus in order to realise and sustain an enhanced and competitive level of return from their investment in developing new medicines.

Key points

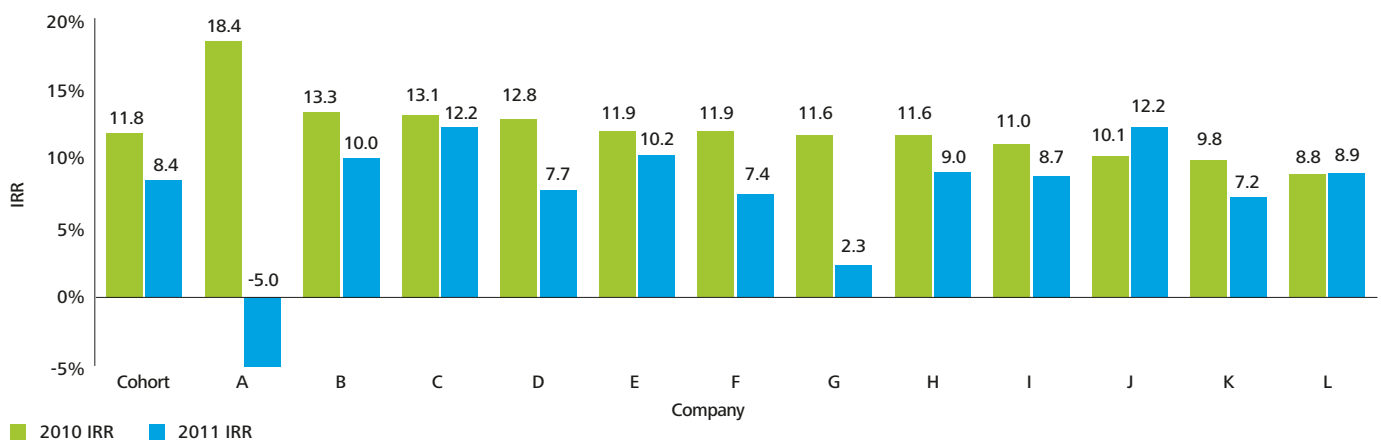
- R&D leaders are under continued pressure to justify the investment in the 'business of R&D'.
- 10 of the 12 companies in our study cohort have seen a decline in returns, resulting in a cohort IRR of 8.4% for 2011 compared to 11.8% last year.
- Year on year (static) IRR measures reflect the productivity challenges within the industry but also conceal underlying successes.
- Analysis of dynamic returns allows us to identify encouraging signs within the industry, but also shine a light on areas of concern which should remain a focus for R&D leaders.

1. Peer benchmarks

Static snapshot

Last year, we developed a performance snapshot of the top 12 research-based pharmaceutical companies (by R&D spend) on 1 January 2010 to baseline R&D IRR. One year on, we see some significant movements in IRR, highlighting that a snapshot or static IRR measure unsurprisingly does not tell the full story of R&D returns.

Figure 1. Comparison of IRR results: 2010* – 2011



*Companies labelled A through to L based on 2010 IRR value. See Appendix 2 for details of the IRR calculation methodology

Source: Deloitte and Thomson Reuters research

10 of the 12 companies in our cohort have seen a fall in IRR this year, resulting in a cohort IRR of 8.4%, compared with 11.8% last year, a reduction of almost 30%. The reasons behind movements in IRR are multifaceted:

- Late stage failures, either through company originated termination or regulatory rejection.
- Successful commercialisation of late stage products: our methodology includes revenue forecasts for products that are in the late stage portfolio (phase III or submission), not those that have been commercialised over the past year. For this reason, a drawback of the static IRR measure is that it does not distinguish a loss of value from product commercialisation, what we term a 'positive loss', from a loss of value due to products that have failed at a late stage in development.

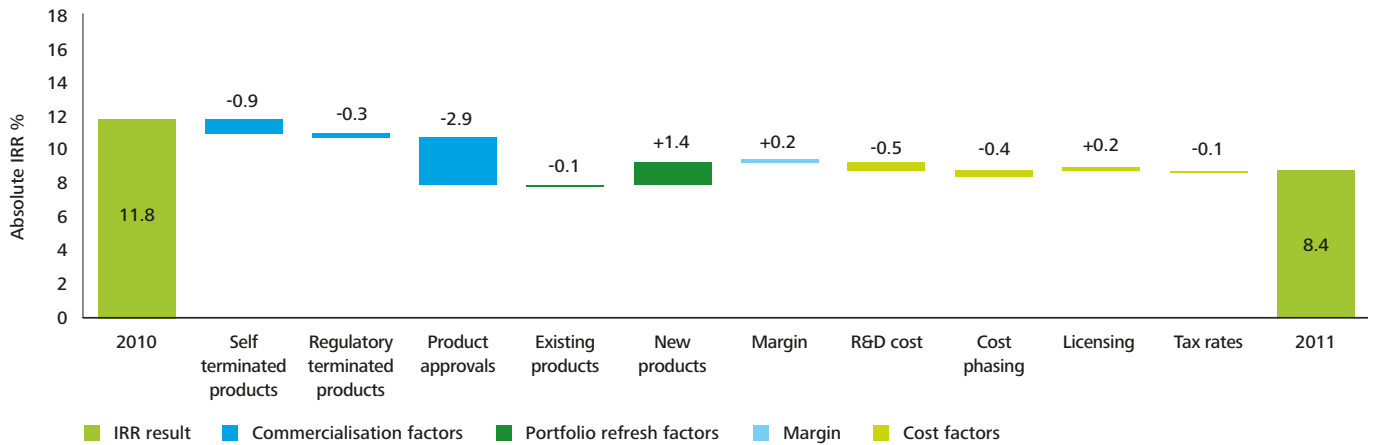
- Revised revenue forecasts of existing late stage products (those that appear in both the 2010 and 2011 late stage portfolios).
- The number and commercial potential of new assets coming into the late stage portfolio between 1 January 2010 and 1 January 2011.
- Changes to R&D costs over the 10 years to 1 January 2011 compared with the 10 years to 1 January 2010.

In order to better reflect these changes, we have defined, measured and assessed the dynamic returns performance of the top 12 pharmaceutical companies to understand the factors that are driving changes in R&D returns year-on-year.

One year on we see some significant movements in IRR, highlighting that a snapshot or static IRR measure does not tell the full story of R&D returns.

Dynamic IRR

Figure 2. Components of dynamic returns 2010 – 2011 at the cohort level

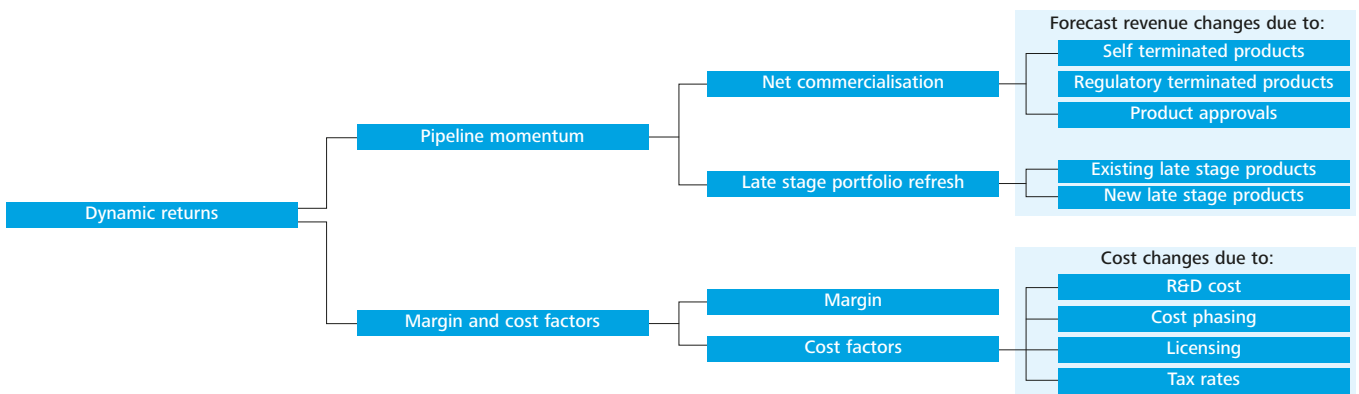


See Appendix 2 for definitions of the factors shown in this figure.

Source: Deloitte and Thomson Reuters research

Figure 2 illustrates the factors that make up dynamic returns at the cohort level. These same factors apply when examining the anatomy of dynamic IRR for an individual company. Dynamic returns can be analysed across two dimensions: pipeline momentum and margin and cost factors (Figure 3).

Figure 3. Components of dynamic returns



Source: Deloitte research

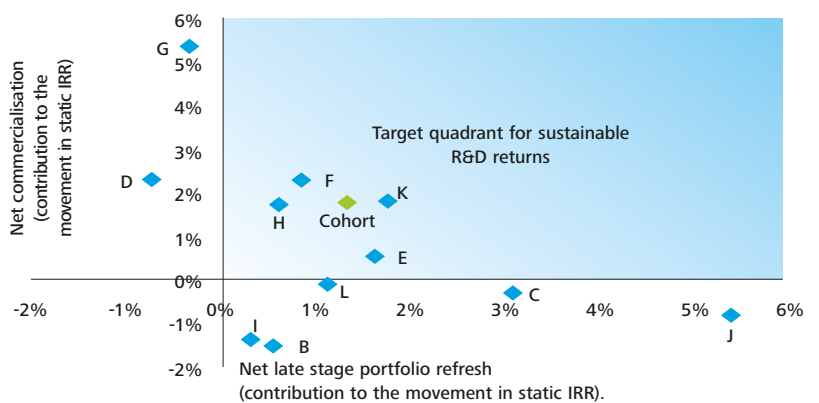
Pipeline momentum

To explain changes in forecast revenue, we look at pipeline momentum, which is made up of two factors that we term 'net commercialisation' and 'net late stage portfolio refresh'.

- Net commercialisation is made up of the approvals from successful commercialisation (positive losses) of products from the late stage portfolio less losses from late stage product failures, against the 2010 baseline.
- Net late stage portfolio refresh is the sum of changes to revenue forecasts for existing late stage products and incremental forecast revenue due to new products entering the late stage portfolio, against a 2010 baseline.

To ensure attractive and sustainable R&D returns, companies need to perform consistently well on both elements of pipeline momentum. Companies that do so will appear in the target quadrant in Figure 4. After one year, less than half of our cohort features in the target quadrant of performance.

Figure 4. Pipeline momentum by company and cohort



◆ Cohort ◆ Individual companies

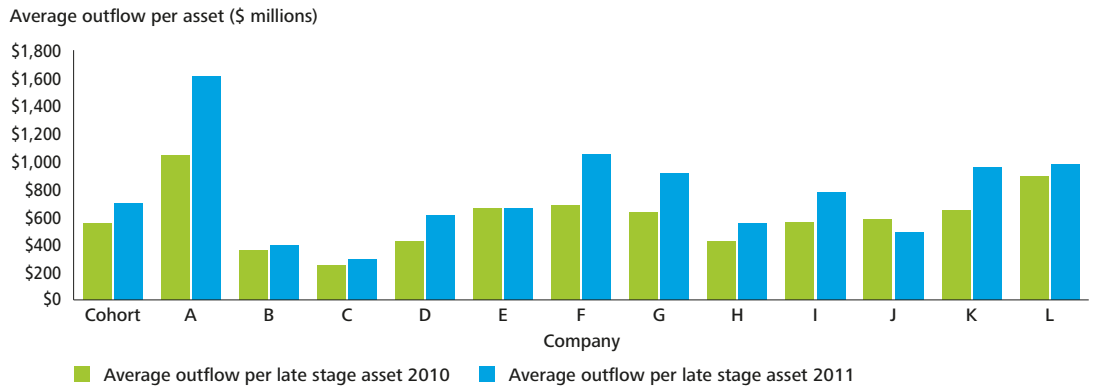
Company A not shown.

Source: Deloitte and Thomson Reuters research

Margin and cost factors

At the cohort level, the average outflow per late stage asset has increased by 25% from 2010 to 2011. Our analysis suggests that this is a combination of increased R&D costs and a reduced number of assets within the late stage portfolio. The result is a small, downward pressure on IRR at the cohort level.

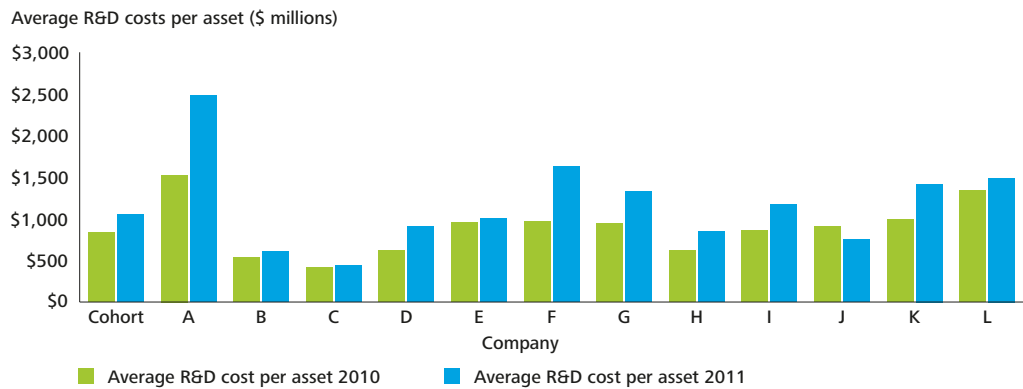
Figure 5. Average outflow per late stage asset*



Source: Deloitte and Thomson Reuters research

The average outflow per asset represents the average cost across the cohort to bring a product from discovery to the late stage portfolio. We risk adjust the average outflow per asset by phase III and submission success rates to estimate the average cost for full product development (R&D costs from discovery through to late stage development). Figure 6 shows that for our cohort of companies, the average cost of successfully bringing a product to market has increased by 21% from \$830 million in 2010 to \$1,048 million in 2011. Notably, there is a wide variation from company to company, from \$439 million to \$2,477 million (see Appendix 1, Table 1).

Figure 6. Average R&D cost per asset

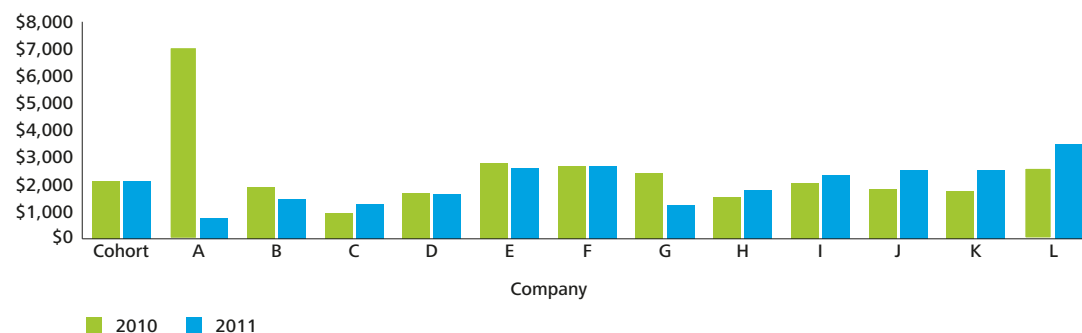


Source: Deloitte and Thomson Reuters research

Rising costs on their own are not a cause for concern if the value generated from these assets also increases. However, our analysis shows that the average inflow per late stage asset at the cohort level is no greater than last year (Figure 7).

Figure 7. Average inflow per late stage asset*

Average inflow per asset (\$ millions)



Source: Deloitte and Thomson Reuters research

Insights from our dynamic returns analysis

Our analysis of dynamic returns highlights mixed performance at both the company and cohort level. Although a single year IRR movement is insufficient to provide a definitive view of performance, we are already seeing the cohort separate with respect to best in class performance.

Encouraging signs that R&D is earning its investment:

- Across the cohort as a whole, the value contribution due to product approvals (a 'positive loss' of IRR) outweighs by a factor of two the value leakage from late stage failures and reduced revenue forecasts for existing products.
- Of the 12 companies that we have analysed, two thirds have performed well on net commercialisation (Figure 4). That is they have generated more value from product commercialisation than they have lost from late stage product failures.
- At the cohort level, non-R&D costs have declined, resulting in a higher operating margin, which helps to free up cash flow that could be reinvested in R&D (see Figure 2). Only two of the 12 companies have seen a decline in margin, i.e. an increase in non-R&D costs, since last year. However, the cohort performs less well in reducing R&D costs.

Areas of concern for R&D leaders:

- Companies need to perform consistently well on both elements of our pipeline momentum measure (see the target quadrant, Figure 4) over a multi-year timeframe in order to generate sustainable value from R&D. After one year, more than half of our cohort is failing to achieve positive performance on both the commercialisation and refresh elements of pipeline momentum.
- The rate of late stage failures is still too high, driving up the average cost to successfully bring a product to market. Given the duration of new pharmaceutical product development it will take several years for the effects of reduced attrition to have a positive influence on new product development costs.
- Cost factors are applying a downward pressure on IRR for all companies. On average, it is costing more to develop each asset in the late stage portfolio (average outflow per asset has increased by 25% across the cohort – see Figure 5). Yet the value of these assets is no greater than those in last year's late stage portfolio (average inflow per asset remains unchanged – see Figure 7). Once downstream attrition is taken into account, this translates into a 21% increase in average R&D cost per asset (Figure 6). Time will tell whether the reduction in the number of late stage assets and the increased average development cost is due to an investment in quality (that is, an increased technical and commercial chance of success).

At just over \$1 billion, it is costing 21% more to develop a new pharmaceutical product on average compared with last year, yet the commercial value of these assets is no greater than last year.

2. R&D transformation: Raising the bar

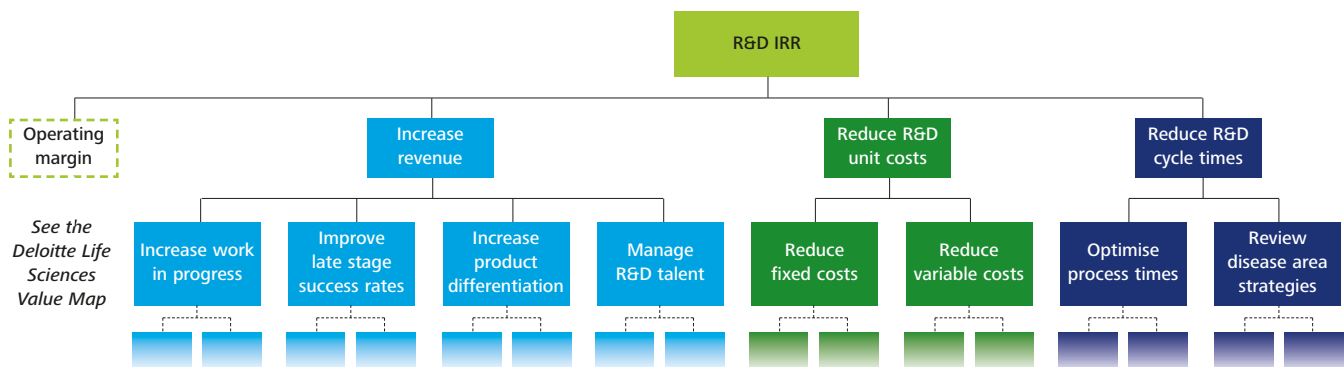
R&D's commercial effectiveness

As findings from our research demonstrate, despite ongoing transformation efforts, greater emphasis needs to be placed on the systemic and relentless pursuit of improved R&D returns. Fundamentally, as R&D leaders know, this will require drug developers to commercialise more products of greater value, faster and at less cost. Whilst the industry is generally targeting the right areas, we anticipate that leading companies will set their sights much higher and target greater change across three broad areas:

- Return on investment rigour in R&D capital allocation and portfolio decisions.
- Collaboration with each other and with payers to realise a material improvement in development success rates.
- Simplification of the business model for new medicine development.

Using Deloitte's Enterprise Value Map for R&D (Figure 8), we highlight improvement opportunities that we see around these three change themes.

Figure 8. Deloitte's Enterprise Value Map for R&D (abbreviated)



Source: Deloitte

Value map: increase revenue

Our study suggests that the average commercial value of each asset in this year's late stage portfolio is unchanged from last year, but against a backdrop of rising development costs per asset. This only increases the pressure from the rest of the business and shareholders on R&D leaders to justify continued investment in the 'business of R&D'.

To be more commercially effective, raise late stage success rates and ensure optimal competitive positioning of pipeline assets, R&D will strive for yet more external focus throughout the value chain by:

- Harnessing innovative opportunities regardless of origination, fostering external as well as internal innovation networks to drive up pipeline value.
- Improving payer, prescriber and patient relationships to improve line of sight between protocol and defined health outcomes.

Innovation performance will be increased by:

- Fully implementing the intent to reduce the distinction between internally and externally sourced innovation in capital allocation decision making.
- Establishing return on investment centres of excellence that bring together analytics, modelling, finance and portfolio management capabilities to support portfolio decisions.
- Using multiple approaches to increase the opportunities for harnessing external innovation, e.g. establishing early stage alliances, forming joint ventures or risk-sharing partnerships.
- Sharing across companies scientific insights regarding failed assets and studies in early development.
- Nurturing a scientific ecosystem that accesses the best scientific talent to better identify and research the most promising assets to progress, regardless of origin.
- Refreshing the R&D talent pool to build out new skills and capabilities that reflect the heightened value and commercial focus that is needed to complement outstanding scientific talent.
- Fostering knowledge sharing between development teams by building a 'corporate innovation memory'.

Line of sight between protocol and defined health outcomes will be improved by:

- Understanding and responding to regulator and payer value criteria earlier in the R&D process.
- Using real world evidence to shape development programme design and build an evidence-based, differentiated health economics case to payers.
- Reconfiguring development strategy in anticipation of greater uptake of outcomes-based reimbursement. Drug developers that are adept in articulating the relative value of their products and in demonstrating a willingness to take on risk, will be seen as more differentiated and more closely aligned with payer needs, even if outcomes-based reimbursement is not consistently adopted by payers.
- Establishing an agile governance approach that encourages development programmes to adapt to the requirements of external stakeholders based on a continued dialogue with them.

Value map: reduce R&D unit costs

Our analysis shows that in the 10 years to 1 January 2011, the average cost to develop a successful product has increased by 21% to \$1,048 million compared with the 10 year period to 1 January 2010. This is despite a concerted effort by most of the industry to reduce R&D expenditure year on year. A large element of cost per successful launch is due to the 'sunk' investment in failed products. The R&D engine needs to be much leaner, certainly until this burden of attrition is worked through. To date, organisations have commonly looked at outsourcing of non-core functions and utilisation of low cost locations to bring down the cost of R&D. However, these measures, while necessary, are not sufficient alone.

Going forward, we believe that R&D leaders will be much more radical in their approach to R&D cost reduction:

- Building on the first generation of outsourcing relationships to realise greater and more sustainable improvements in cost, speed and quality of delivery, for example through:
 - Sponsor organisations coming together to identify areas where ways of working and tools could be simplified and standardised collectively, thereby promoting the achievement of scale economies within a common service provider.
 - Incentivising collaborative working and increasing visibility across organisation boundaries between provider and sponsor to foster innovative thinking and identify opportunities for cost, speed and quality improvements to the benefit of both parties.
 - Sponsor and service provider organisations putting in place joint transformation teams and governance structures to shape and follow through on performance improvement opportunities anchored around a business case for change.
- Collaborating with peer companies to share and co-source non-competitive development capabilities in the form of people, processes, tools and facilities, for example, common clinical monitoring resources or selected clinical information technology and support functions, thereby driving up capacity utilisation.

R&D leaders will be more radical in their approach to cost reduction, collaborating with each other to share and to source non-competitive drug development capabilities.

- Making strategic tax planning decisions at a global and local level, to ensure that IP is held in locations which provide the most favourable tax status for income from licensing or sales.
- Optimising clinical trial planning:
 - To reduce under- and over-recruitment.
 - To reduce the number of non-enrolling sites.
 - To reduce study complexity.

Value map: reduce R&D cycle times

A reduction in cycle times may be driven by more focused governance, process improvement or more selective disease area strategies.

Given the interdependency of revenue, cost and cycle times, approaches to accelerate development are typically realised in combination with approaches to either increase revenue and/or reduce R&D costs:

- Applying lean process improvement, to reduce the ‘white space’ between development phases and shorten the critical path to regulatory submission.
- Improve identification of clinical trial participants and investigator selection through developing and enhancing relationships with healthcare providers.
- Selecting disease areas within the portfolio based on depth of scientific expertise and understanding, disease area cycle times, degree of unmet need, patient saturation and market potential.

Simulating returns improvement

As an aid to selecting transformation priorities, we conducted an IRR simulation on a mid quartile company. The simulation explored the change required in the six high level levers to affect a relative 10% change in IRR (Figure 9).

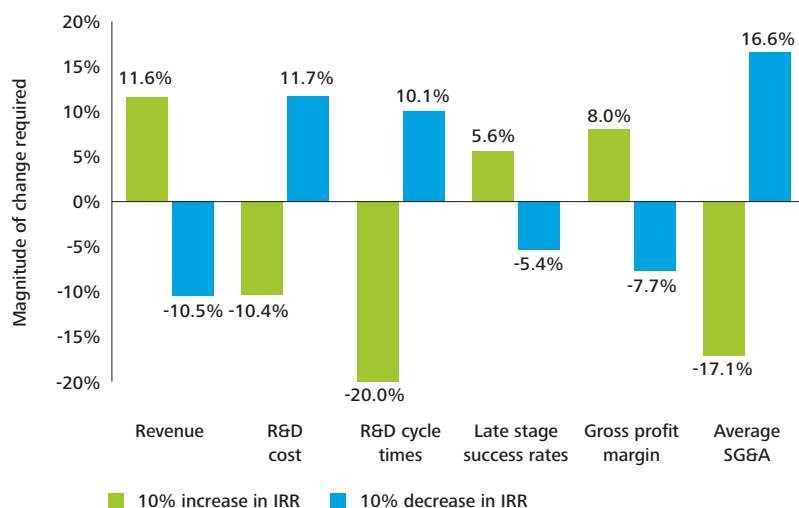
Our simulation suggests a relatively low magnitude of change in late stage success rates compared to other levers can have an equal impact on R&D returns, emphasising the need to focus on quality of output and not just cost. As previously highlighted, improved payer, prescriber and patient focus to improve line of sight between protocol and outcomes alongside improved focus on personalised medicines strategies are just some of the means to increase this quality of output and improve late stage success rates.

Due to the relatively lower total expenditure of pharmaceutical companies on SG&A relative to the other major cost areas, a greater change is required to impact IRR by 10%.

Notably the analysis shows that movements in the gross profit margin have the second highest impact on IRR; from this it would appear that even modest efforts to improve manufacturing efficiency and maintain low raw material costs will, over a period of time, have a profound impact on returns.

Both the SG&A and Gross Profit Margin simulation examples demonstrate how improvements in these areas will enhance IRR, highlighting that all corporate functions have a role to play in helping R&D to earn its investment.

Figure 9. Change in value levers required for an increase or decrease in IRR of 10%



See Appendix 2 for the sensitivity analysis methodology.

Source: Deloitte and Thomson Reuters research

3. Conclusions

Our analysis of R&D IRR performance over the past year has shown significant movements in the static IRR measure, with most companies in our cohort showing a reduction in static IRR. In some cases, this is because the companies have experienced real declines in their ability to prime the late stage portfolio with valuable assets that have a high technical and commercial probability of success, while in other cases, the reduction in IRR conceals product commercialisation achievements. Thus, we believe the static IRR measure alone needs to be viewed in tandem with the factors contributing to the movements in IRR performance. In addition, the contribution of non-R&D functions cannot be overlooked when considering R&D returns, as highlighted by the findings of our returns simulation.

Relative to a 10 to 12 year development cycle in pharmaceutical R&D, one year's movement in static returns is insufficient to give a fair account of performance. Nonetheless, we see areas for concern one year on:

- Imbalance on the elements of pipeline momentum: late stage terminations are taking out too much value and are not adequately compensated for by late stage refresh rates (improvements in existing late stage products and new products entering the late stage portfolio).

- The late stage failure rate is still too high and successful products continue to bear the cost of those that have failed at an unsustainable level.
- Development costs per asset have increased with fewer assets now populating the late stage portfolio. Time will tell whether the reduction in the number of late stage assets and the increased average development cost is due to an investment in quality (i.e., increased technical and commercial probability of success).

R&D leaders need to demonstrate real improvements in these areas in order to shore up confidence in the ability of R&D to earn its investment. We believe they can do this by raising their level of ambition in three key areas:

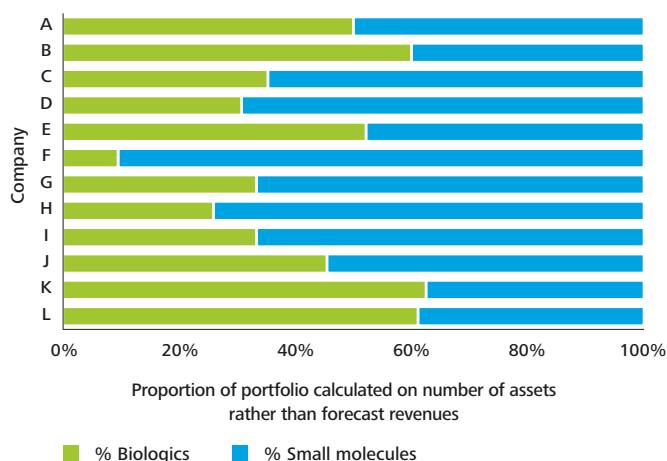
- Embedding greater return on investment rigour in capital allocation decision making.
- Collaborating more intensively with peers and with payers.
- Simplifying the fundamentals of R&D operations.

R&D leaders need to demonstrate real progress in key areas in order to shore up confidence in R&D's ability to earn its investment.

Appendix 1: Data analysis

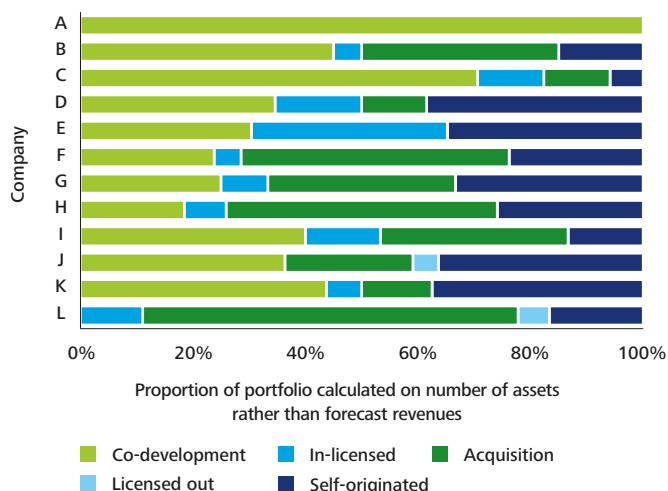
No single attribute on its own can explain IRR performance relative to the peer group.

Figure 10. Late stage portfolio: biologics vs. small molecules



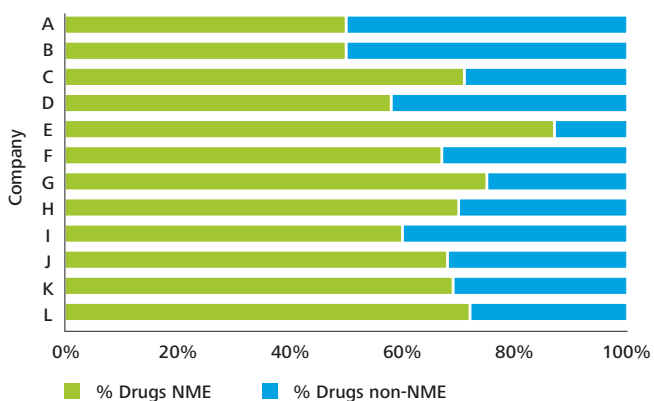
Source: Deloitte and Thomson Reuters research

Figure 12. Late stage portfolio: origination



Source: Deloitte and Thomson Reuters research

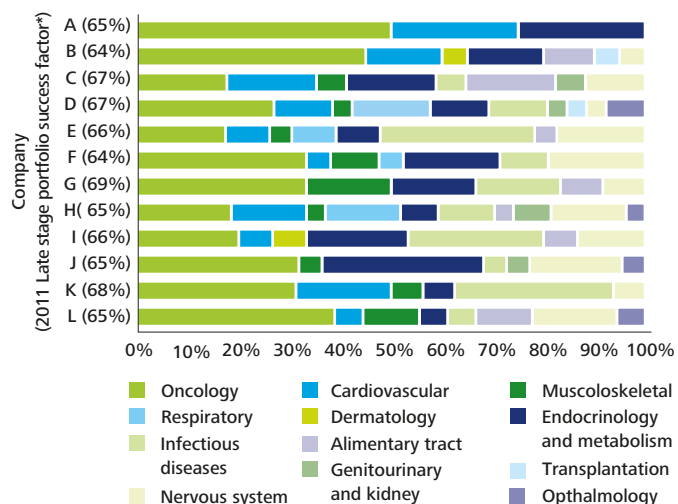
Figure 11. Late stage portfolio: new molecular entities (NMEs) vs. non-NMEs*



*Non-NME defined as a chemical, biological or biotechnology substance that has previously been marketed and is under development as a formulation or new dosage form in the same indication. This definition also includes chemical, biological or biotechnology substances which are already marketed in one indication but currently under development for further indications under the same or different brand names. Examples include reformulations and line extensions. **Proportion of portfolio calculated on number of assets rather than forecast revenues.**

Source: Deloitte and Thomson Reuters research

Figure 13. Late stage portfolio: therapeutic area focus



*The late stage portfolio success factor is the combination of the phase III and submission success rates across the late stage portfolio.

Proportion of portfolio calculated on number of assets rather than forecast revenues.

Source: Deloitte and Thomson Reuters research

Table 1. Average R&D costs

Company	Average outflow per asset 2011	Late stage portfolio success factor*	Average R&D cost 2011**	Change in average R&D cost 2010 – 2011
Cohort	\$692	66%	\$1,048	21%
A	\$1,614	65%	\$2,477	38%
B	\$390	64%	\$611	12%
C	\$295	67%	\$439	6%
D	\$607	67%	\$904	31%
E	\$660	66%	\$999	4%
F	\$1,045	64%	\$1,629	40%
G	\$915	69%	\$1,326	29%
H	\$553	65%	\$850	27%
I	\$775	66%	\$1,171	26%
J	\$485	65%	\$746	-21%
K	\$957	68%	\$1,418	30%
L	\$976	65%	\$1,490	10%

*The late stage portfolio success factor is the combination of the phase III and submission success rates across the late stage portfolio.

**Average R&D cost per asset (from discovery to launch)

Source: Deloitte and Thomson Reuters research

Appendix 2: Our methodology

Company cohort definition

We used the same cohort as in last year's report, i.e. the top 12 research-based pharmaceutical companies, measured by R&D spend in 2008/09. These companies are: Pfizer, Roche, Novartis, Sanofi-Aventis, GlaxoSmithKline, Johnson & Johnson, AstraZeneca, Merck & Co. Inc., Eli Lilly, Bristol-Myers Squibb, Takeda and Amgen.

We have made some refinements to the models developed last year that have consequently led to some minor changes in the performance ranking (which was not disclosed in the public domain). 2010 IRR values have been amended in this report where applicable.

Principles applied to the model

General

2011 Internal Rate of Return (IRR) has been calculated on the late stage portfolio as of 1 January 2011, using 10 years of annual outflows (1 January 2001 through to 31 December 2010) and 21 years of forecast annual inflows (1 January 2011 through to 31 December 2031). The model calculates IRR using post tax cash flows.

Late stage is defined as compounds that were either in phase III or submitted as at 1 January 2011. The following types of compounds have been included within the company late stage product portfolios:

- new chemical entities;
- new biological entities;
- line extension products; and
- reformulations.

Foreign currency

All calculations have been performed in US dollars. Where historic source data has been presented in currencies other than US dollars, they have been translated using the Financial Times yearly average rate applicable to 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.

Taxation

IRR has been calculated based on post tax inflow and outflows. Company specific tax rates have been computed based on average effective tax rates over the 10 years to 31 December 2010, adjusted for non-recurring items (e.g. litigation costs, impairments, in-process R&D expense).

Forecast revenues

1. Company revenues were forecast over the period 1 January 2011 to 31 December 2031.
2. All revenue data was extracted from Thomson Reuters' assets and proprietary modelling techniques. Data consistency was checked with external data sources and websites for consistency and agreement with general market principles (e.g. www.fiercebiotech.com).
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 1994-2009). 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' consensus forecast data, combined with a proprietary sales forecast model. This tool used consensus forecast data as basis in tandem with a weighted sales average of the previous three years of sales data to calculate the desired year's sales data. Sales uptake curves were modelled using this methodology combined with an assessment of a compounds individual characteristics (e.g. molecule type, indication, Mechanism of Action and target) to understand if a compound had high, medium or low sales potential.

5. After peak sales had been reached, standard erosion curves were applied dependent on the molecule type (e.g. small molecule or biologic). To reflect a more real world this year with regard to sales erosion from loss of IP exclusivity, 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 place 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 place is likely to have a less profound effect around loss of sales for biologics. Therefore we see the use of two different curves which reflect real world realities of sales loss to patent expiration as an incremental improvement. This may cause some differences in sales forecasts on a per molecule basis, however it will not explain the global changes observed in IRR within the paper. It is also important to note that each revenue forecast is reviewed on yearly basis and adjusted dependent on new data available.

6. Small molecule and biologic curves are as follows (please refer to Figure 14):

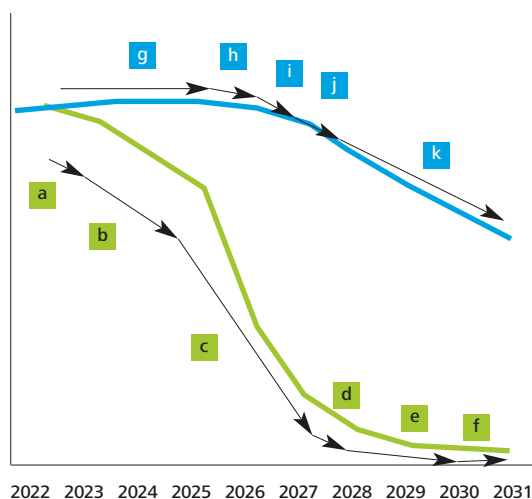
For small molecules

- a. A 5% decrease in sales 2-3 years prior to patent expiration.
- b. A 10% year on year decrease in sales for 2 years prior to patent expiration.
- c. Once patent expiration occurred a 50% year on year decrease in sales for 4 years.
- d. A 25% decrease in sales for 1 year.
- e. A 10% decrease in sales for 2 years.
- f. A 5% decrease in sales from thereafter until 2030.

For biologics

- g. No decrease in sales to patent expiration.
- h. A 2% decrease in sales for 1 year.
- i. A 5% decrease in sales for 2 years.
- j. A 9% decrease in sales for 1 year.
- k. A 10% decrease in sales until 2031.

Figure 14. A diagrammatic representation of small molecule and biologic sales erosion curves



7. 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 biologics. It is therefore assumed that erosion of biologics sales will be considerably smaller compared with that of small molecules.

8. Available patent information was extracted from Thomson Pharma 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 patent expiration date in Newport was given precedence based on patents for major markets (USA, Europe and Japan) All patents relating to a compound were considered when defining patent expiry.
- b. Product patents were used as the primary source for definition of a patent expiry date.

- c. Where product patent information was inconclusive secondary patents were used to define patent dates.
- d. For reformulations and line extensions other patent types were used to understand where 5 year patent extensions were appropriate.

Margin applied to forecast revenues (Inflows)

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 10 years to 2010, adding back R&D expense and depreciation/amortisation, and deducting capital expenditure and non-recurring costs.
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 period from 1 January 2001 to 31 December 2010 are assumed to equate to future margins over the 21 year revenue forecast period.

R&D outflows

For all compounds included within company late stage portfolios, the origin of the compound was assessed; compounds were categorised as either 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 in-process 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 10 year period. Benchmark data (Source: CMR International 2010 Pharmaceutical R&D Factbook) was used to allocate costs as shown in Figure 15.

Compared with last year, industry average cycle times remain unchanged while cost allocation has changed as shown in Table 2.

Table 2. Change in cost allocation.

Company	2010 Report	2011 Report
Discovery to first toxicity dose	25%	25%
Pre-clinical to Phase II	20%	29%
Phase III and submission	55%	46%

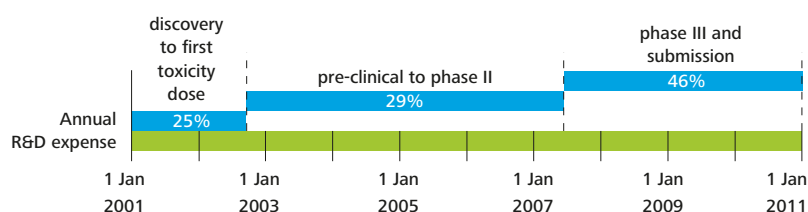
This methodology incorporates the cost of attrition of assets from the initial cohort at discovery to the late stage portfolio as at 1 January 2011.

5. R&D costs have not been included within the model beyond 31 December 2010.

Compounds acquired through in-licensing

1. Where a compound included within the company late stage product portfolios has been in-licensed from a 3rd party, any upfront payments have been included in the relevant year of acquisition.
2. In-licensing information was obtained from the Thomson Reuters Pharma partnering deals database. 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.

Figure 15. Benchmarked R&D costs and cycle times



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 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.

Dynamic IRR methodology

Dynamic returns (see Figure 2) reconcile the movement in absolute return from 1 January 2010 to 1 January 2011. This takes nine key factors and calculates the effect of each individually on the IRR movement. These are divided into inflow factors and outflow factors.

Commercialisation and portfolio refresh factors

There are five reasons why inflow associated with late stage portfolio products would change periodically:

- 'Self-terminated' products and 'regulatory terminated' products': Removal of future revenues associated with products terminated during the year;
- 'Product approvals': Removal of future revenues associated with products approved during the year;
- 'Existing products': Increased/reduced forecast revenues relating to products remaining in the portfolio;

- 'New products': New revenues associated with products entering the late stage portfolio; and
- 'Margin': A change in the average cash operating margin.

The annualised impact of each of these conditions on the cash inflow has been input into the 2010 model in isolation in order to quantify the effect on the IRR, given constant outflows.

The operating margin has been shown as a separate factor, as opposed to incorporating into the revenue changes, to increase visibility of this factor.

Cost factors

There are four outflow factors that affect the IRR movements:

- 'R&D cost': Changes to R&D costs for self originated compounds.
- 'Cost phasing': An update in the methodology used for allocating R&D costs over the 10 year historical period (see Figure 15 and Table 2).
- 'Licensing': Changes to outflows related to in-licensing costs.
- 'Tax rates': Changes to the company specific tax rates based on the average effective tax rates over the historical 10 year period.

The annual outflow impact of each of these conditions has been input into the 2010 model in isolation in order to quantify the effect on the IRR, given constant inflows.

Sensitivity analysis

Sensitivity analysis was conducted across three high level R&D value levers (revenue, cost and cycle times) to bring about a 10% 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 10 year period.

- **Cycle times:** we calculated the effects of cycle time changes 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. Peak revenues are increased to take into account the earlier launch dates of the portfolio of assets.
 - 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 10% increase/decrease in IRR.

Challenges associated with the model

The use of revenue forecast data and publicly available information regarding deal information presents certain challenges and risks associated with the construction of revenue forecasts and distribution of R&D costs within the pharmaceutical industry. These challenges and risks are the following:

1. 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;
2. The revenue and portfolio information provided in this paper constitute forward looking statements relating to the financial, operational and performance of specific companies. Although the authors of this paper 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;
3. All forward looking statements reflect knowledge and information available as of 1st January 2011 and may not be updated post publication;
4. In-licensing costs included in the model are limited to those products included in the late stage portfolio, thus in-licensing costs associated with products that failed prior to Phase III are not included;
5. 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 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;
6. Forecast R&D costs have not been included within the model beyond 31 December 2010 as accurate and relevant information is not available;
7. The assumption that average cash operating profits over the period from 1 January 2001 to 31 December 2010 equate to future margins over the 21 year revenue forecast period may fail to fully reflect the impact of recent corporate cost reduction initiatives;
8. 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;
9. The model is sensitive to the distribution of products across the late stage portfolio (phase III to submission) and as this drives cash flow timing, a snapshot taken in a different year could generate different results; and
10. 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 we expect; 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.

Appendix 3: Glossary

Average R&D cost per asset: the average cost to fully develop a product from discovery to commercialisation, calculated by risk adjusting the average outflow per asset by phase III and submission success rates.

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

Cost phasing: refers to the use of industry average cycle times and cost allocation when calculating R&D cost over the 10 year period to 31 December 2010. Details of the phasing and cost allocation can be found in Appendix 1 (Figure 15 and Table 2). Compared with last year, industry average cycle times remain unchanged, while cost allocation has changed which may account for some of the changes to static IRR from 2010 to 2011. Changes in phasing contribute to the 'margin and cost factors' dimension of 'dynamic returns'.

Dynamic returns: reconcile the movement in year on year or 'static IRR' from 1 January 2010 to 1 January 2011.

Existing products: one of the 'net late stage portfolio refresh' factors which make up 'dynamic returns'. Existing products appear in company pipelines as of 1 January 2010 and 1 January 2011, although revenue forecasts may have changed between the two snapshot dates due to additional information being available on the product/indication.

Inflows: determined by applying an average cash operating 'margin' to risk adjusted revenues over the 21 year forecast period.

IRR/static IRR/static returns: calculated on the 'late stage portfolio' as of 1 January 2011, using 10 years of historical annual outflows (1 January 2001 to 31 December 2010) and 21 years of forecast annual inflows (1 January 2011 to 31 December 2031). The model calculates IRR using post tax cash flows. Essentially IRR is the discount rate which makes the net present value of the cash flows expected for an investment equal to zero. An IRR equates (on a present value basis) the cost of an investment and the expected benefits.

Late stage portfolio: compounds that were either in phase III or submitted for regulatory approval as of 1 January 2011.

Late stage terminations/failures: one of the 'net commercialisation' factors which make up 'dynamic returns'. Late stage terminations refer to products terminated in phase III or submission through either regulatory rejection (see 'regulatory terminated') or an internal company decision (see 'self terminated').

Licensing/in-licensing: costs associated with in-licensing products within the 'late stage portfolio', where details are available in the public domain. Any upfront payments are included in the relevant year of acquisition. As publically available data typically does not include the timing or quantum of future contingent payments, the total amount of these costs has been assumed to have occurred at their maximum potential amounts in the forecast year of commencement sales. Changes in licensing contribute to the 'margin and cost factors' dimension of 'dynamic returns'.

Margin: the average cash operating margin has been calculated using reported operating profit over the past 10 years to 31 December 2010, adding back R&D expense and depreciation/amortisation, and deducting capital expenditure and non-recurring costs. Future margins over the 21 year revenue forecast period are assumed to equate average cash operating profits over the period from 1 January 2001 to 31 December 2010. Changes in margin contribute to the 'margin and cost factors' dimension of 'pipeline momentum'.

Margin and cost factors: one of the dimensions of 'dynamic returns'. This dimension illustrates changes in margin and cost factors such as 'R&D cost', 'phasing', 'licensing' and 'tax rates' from one snapshot to another.

Net commercialisation: the sum of 'positive losses' from product approvals and losses due to 'late stage terminations'.

Net late stage portfolio refresh: the sum of increased revenue forecasts due to new products entering the 'late stage portfolio' and changes to revenue forecasts for the existing late stage products.

New products: one of the 'net late stage portfolio refresh' factors which make up 'dynamic returns'. New products are those that appear in the portfolio as of the 1 January 2011 snapshot, but were not part of the company pipeline 1 year previously. Forecast revenues associated with these products are included in the static IRR calculation for this year.

Outflows: are assumed to equal R&D costs (as provided by company profit and loss accounts), unless a non-cash expense is separately disclosed in which case this is excluded from the R&D cost.

Pipeline momentum: one of the dimensions of 'dynamic IRR' or 'dynamic returns'. Pipeline momentum explains the changes in forecast revenue from one snapshot to another and is a combination of 'net commercialisation' and 'net late stage portfolio refresh'.

Positive loss: a loss of value contribution to the 'static IRR' measure due to product commercialisation (thus taking the product out of the late stage portfolio).

Product approvals: one of the 'net commercialisation' factors which make up 'dynamic returns'. Approved products are those products that were part of the pipeline snapshot taken on 1 January 2010 but that are no longer in the late stage portfolio as of the 2011 snapshot because they have been commercialised in 2010 in at least one major market. Future revenues for these products are not included in the 'static IRR' calculation for this year.

Regulatory terminated products: part of the 'net commercialisation' dimension of 'dynamic returns'. Regulatory terminated products are those products that were part of the pipeline snapshot taken on 1 January 2010 but no longer appear on 1 January 2011 due to regulatory rejection. Future revenues for these products are not included in the static IRR calculation for this year.

R&D cost: determined using company reported R&D expense on profit and loss accounts. Changes in R&D costs contribute to the 'margin and cost factors' dimension of 'dynamic returns'.

Self terminated products: part of the 'net commercialisation' dimension of 'dynamic returns'. Self-terminated products are those products that were part of the pipeline snapshot taken on 1 January 2010 but no longer appear on 1 January 2011 due to a company decision to terminate development. Future revenues for these products are not included in the static IRR calculation for this year.

Success factor: the combination of the phase III and submission success rates across the 'late stage portfolio'.

Tax rates: company specific tax rates have been calculated based on average effective tax rates over the 10 years to 31 December 2010, adjusted for non-recurring items (e.g. litigation costs, impairments, in-process R&D expense). Changes in tax rates contribute to the 'margin and cost factors' dimension of 'dynamic returns'.

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