White Paper

A New Look at R&D Productivity

How small changes to key levers can dramatically impact cost per output.

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Introduction

Pharmaceutical company R&D productivity has been a topic of concern among analysts over the last 10-to-15 years. During much of this period, the volume of new product approvals failed to reflect the magnitude of industry R&D investment, despite major technological and scientific advances in areas such screening and genomics. In parallel, it was often not apparent that the value of late-stage pipelines would be sufficient to mitigate the revenue impact of loss-of-exclusivity for key blockbuster products.

A range of factors, internal to individual companies and more generally in the external environment, have previously been implicated in declining R&D productivity[1,2] as shown in Figure 1.

More recently, industry R&D productivity has shown some tangible signs of improvement. Since 2017, the global volume of novel active substance launches has overall been trending positively hitting an all-time high in 2021. Clinical development productivity however — as measured by a composite metric of trial duration, complexity and success — has been in decline.[3]

Figure 1: Factors negatively impacting R&D productivity

INTERNAL FACTORS

- Incentivisation of volume-based research delivery targets, at the expense of quality ('progression-seeking' vs 'truth-seeking')
- Overestimation of the benefits of technology improvements
- Assuming that increased investment will naturally translate into improved productivity
- Increasing clinical trial costs
- Sub-optimal governance processes and decision-making

EXTERNAL FACTORS

- Decreasing risk-tolerance of regulatory agencies
- Higher reimbursement and payer hurdles
- Declining 'low hanging fruit' target opportunities for therapeutic development
- More-challenging Target Product Profile hurdles, resulting from improving standards of care

Modelling R&D productivity and cost per approval

We have developed an R&D productivity model which, in contrast with others:

- Incorporates company specific data rather than using the same underlying 'industry' benchmark data across all companies
- Considers early-stage as well as late-stage R&D
- Enables analyses to be conducted at any of three levels: single-company; comparative across specific individual companies; and industry cohort level in aggregate
- Enables conclusions to be drawn independently regarding the productivity impact of actual and hypothetical changes to R&D

This combination of features means that, rather than simply reporting on aggregate-level industry trends in productivity, the model enables the identification of areas that may be impeding R&D productivity within individual companies, creating the opportunity for targeted improvements and demonstrating the likely impact of these in credible, quantitative terms (Figure 2).

In this paper, using our model, we explore one specific aspect of R&D productivity: the attrition-loaded cost of achieving a new product approval. We also illustrate the dramatic – and demonstrably feasible – cost benefit available when even small changes to key levers in R&D are made.

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Figure 2: IQVIA has built a model to investigate R&D productivity and examine how it can be improved

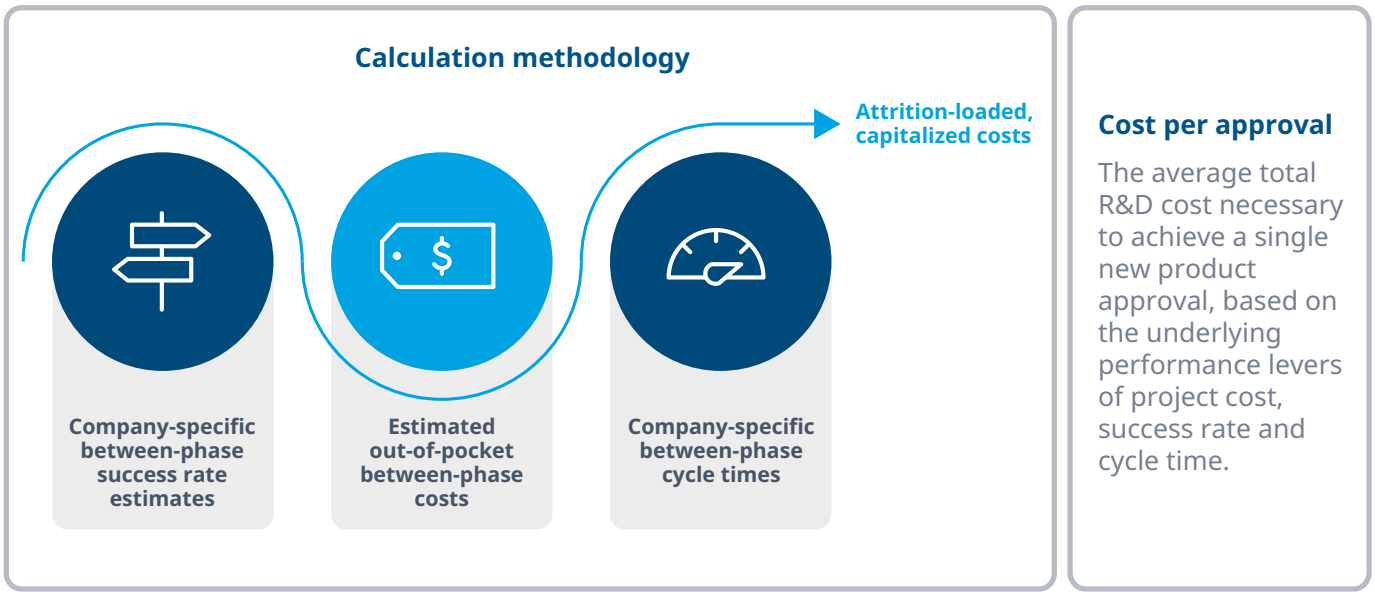
UNLIKE OTHERS, IQVIA'S MODEL WAS BUILT TO ENABLE BETWEEN-COMPANY COMPARISON OF KEY R&D PRODUCTIVITY METRICS, INCORPORATING COMPANY-SPECIFIC LEVERS				
CATEGORY	R&D DATA BREADTH / QUALITY	NAMED-COMPANY REPORTING AVAILABLE	COMPANY-SPECIFIC R&D FUNDAMENTALS	REFLECTS EARLY AS WELL AS LATE-STAGE PIPELINE
ANNUAL INDUSTRY PRODUCTIVITY WHITE PAPERS	🔴	🔴	🔴	🔴
INVESTMENT ANALYST REPORTS	🟠	🟢	🔴	🔴
SYNDICATED BENCHMARKING	🟢	🔴	🟢	🟢
SCIENTIFIC LITERATURE PUBLICATIONS	🔴	🔴	🔴	🟢
IQVIA PRODUCTIVITY MODEL	🟠	🟢	🟢	🟢

Calculating R&D cost per new product approval

In our productivity model cost-per-approval is calculated broadly following the methodological approach described by Paul *et al*, 2010.[4] For a cohort of 14 major pharmaceutical companies, we used company-specific between-phase success rate estimates to back-calculate the number of pipeline assets required in each preceding phase in order to achieve a single asset approval (taking into account pipeline attrition).

We then applied estimated out-of-pocket between-phase costs to each of these prior assets. Finally, we utilised company-specific between-phase cycle time estimates to derive capitalized costs – thereby accounting for the impact of R&D duration on cost. The combined, attrition-loaded, capitalized costs represent the average total R&D cost necessary to achieve a single new product approval, based on the underlying performance levers of project cost, success rate and cycle time (Figure 3).

Figure 3: R&D Productivity measured as the attrition-loaded cost of achieving a new product approval



Trends in cost per approval for major pharmaceutical companies

Our analysis of cost-per-approval for the company cohort demonstrates large differences over the 2017-to-2021 period, as well as dramatic changes within individual companies since 2012-to-2016 (Figure 4).

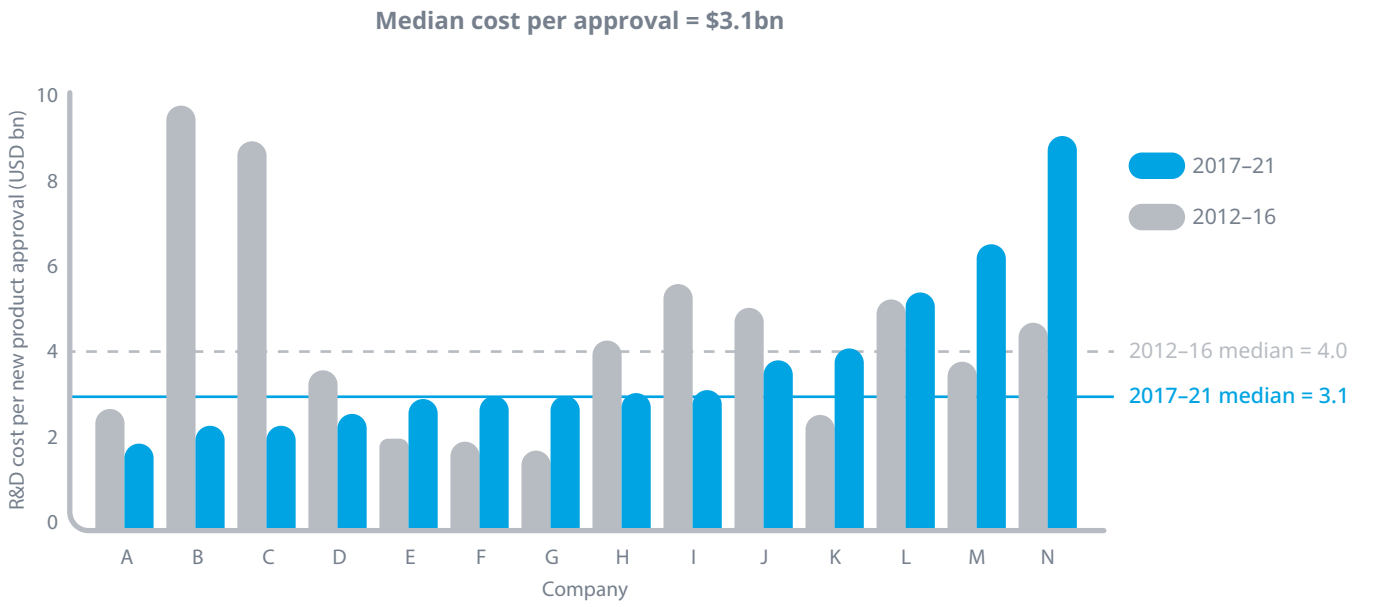
For the most recent period, our collective industry-level figure across the cohort is broadly similar to industry-level estimates of cost per NME approval previously reported by Tufts Center for the Study of Drug Development[5] (when expressed in 2021 dollars) but is slightly higher than that reported by Deloitte using different data and methodologies.[6]

Overall costs at the cohort level have declined in comparison to the preceding five-year period, but this is highly variable at the level of individual companies. Note that this overall cost reduction does not necessarily reflect any reduction in the cost of developing individual assets from one milestone to the next, as portfolio-level factors — such as pipeline attrition — are highly significant in the overall R&D cost.

Top performers in our analysis have achieved cost-per-approval figures of around USD 2bn. Although we have not focused on value metrics in this paper (e.g. revenues or NPV from new and upcoming launches), these top companies should have little difficulty in demonstrating impressive returns on their R&D investment. In contrast, companies in the bottom quartile – with cost-per-approval figures of over USD 5bn – will require higher value assets in order to demonstrate attractive returns from the pipeline.

Importantly, our analysis shows significant changes – both favourable and unfavourable – within individual companies, which can be correlated with publicly-disclosed activities such as targeted R&D enhancements, major acquisitions and portfolio rationalisation (data not shown).

Figure 4: On a spend-per-approval basis, the R&D productivity landscape has shifted considerably for major pharma companies



Source: IQVIA analysis

Large improvements in cost-per-approval can be achieved even with relatively small improvements to underlying levers

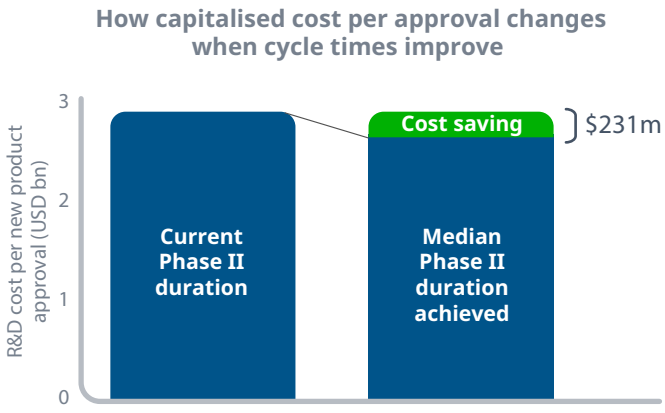
Our analyses show that substantial cost benefits can be released even with relatively modest improvement to underlying R&D levers — and this is especially apparent for companies that have faced historical challenges with respect to one or more of these levers.

THE IMPACT OF IMPROVEMENTS IN CYCLE TIMES

To illustrate, based on our analysis, one of the factors hampering company E's potential to achieve top quartile performance in cost-per-output for 2017–2021 (Figure 4) was a lengthy average Phase II duration. The model shows that if phase II duration was reduced only to the cohort median, it would be possible to save USD 231m from Company E's cost-per-approval figure (Figure 5).

The model can also evaluate the impact of improvements in study-level cycle times. For example, if Company E were to reduce overall average *clinical study* duration by 2 months (we assume a typical development pathway for simplicity) it could save USD 145m in overall cost-per-approval (Figure 6).

Figure 5: Substantial cost savings can be achieved even by companies that are performing well

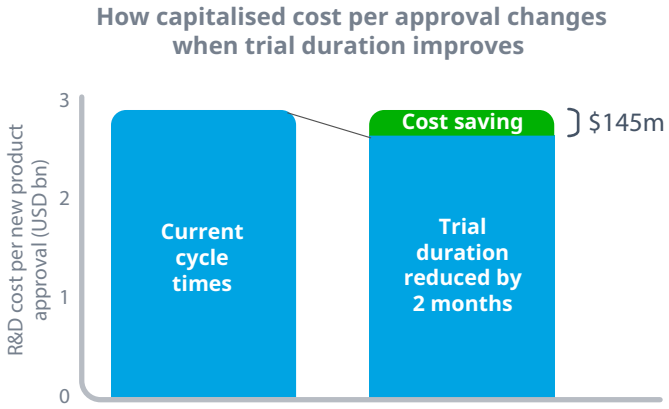


Company E's cost-per-output performance could be improved by reducing its lengthy Phase II cycle time.

Model - Reducing Phase II duration to the cohort median would save $231m from Company E's cost per approval figure.

Source: IQVIA analysis

Figure 6: Modelling the impact on productivity of changes to study cycle times



Model - Company E reduces overall average clinical study duration by 2 months.

Achievable savings of $145m in overall cost per approval.

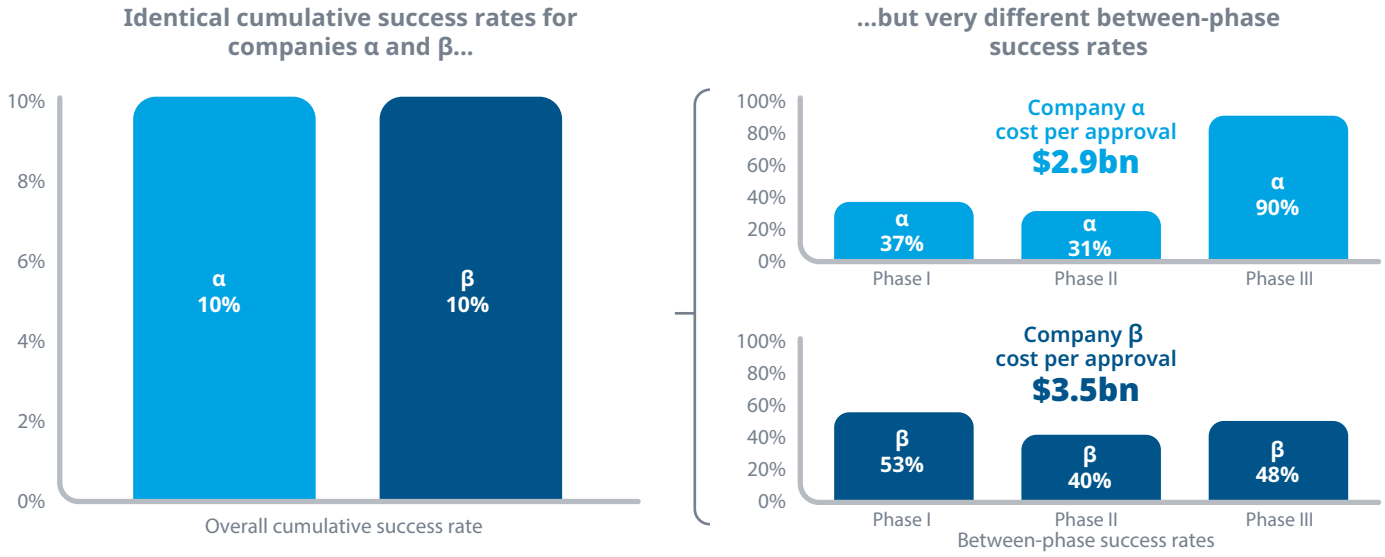
Source: IQVIA analysis.

THE IMPACT OF IMPROVEMENTS IN SUCCESS RATES

Between-phase success rates — defined as the proportion of phase progressions among project fates (progressions to next phase + terminations in phase) over a given period — are critically important levers in modulating cost-per-output performance. However, all attrition is not equal and the impact of success rates on productivity varies by development phase.

Our analyses show that substantial cost benefits can be released even with relatively modest improvement to underlying R&D levers.

Figure 7: The impact of success rates on productivity varies by development phase



Consider Company α and Company β, having identical characteristics:

- **between-phase (per-asset) costs**
- **between-phase cycle times**
- **end-to-end success rates**

But their phase-by-phase attrition profiles differ, dramatically impacting cost

Source: IQVIA analysis.

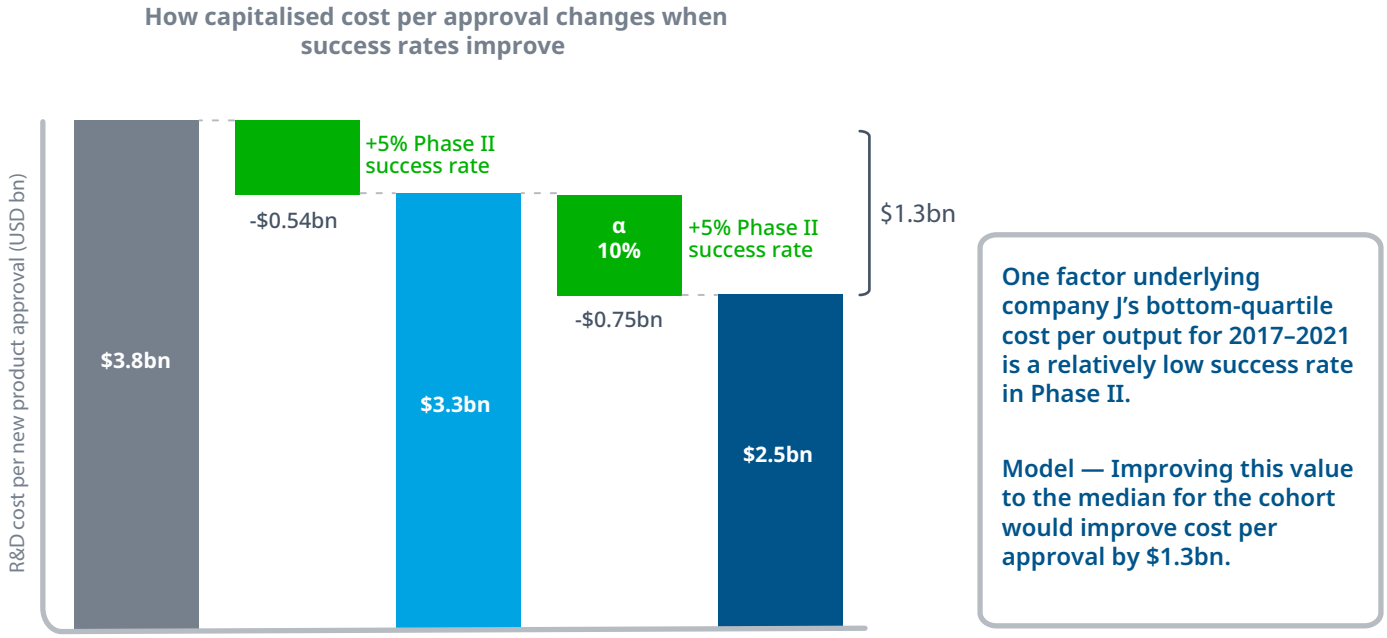
Consider two hypothetical companies — Company α and Company β — that have identical between-phase (per-asset) costs and identical between-phase cycle times (in all cases matching the median for the major company cohort). The two companies also share identical end-to-end success rates of 10% from Phase I start to filing, but different between-phase success rates with very different cost consequences (Figure 7).

Whilst both companies could legitimately claim to have industry median end-to-end success rates, Company α is in a more sustainable productivity position because attrition is weighted towards the early pipeline. In Company β, where attrition is weighted more towards the late-stage portfolio, costs-per-approval are much higher.

This illustration also highlights the importance of an end-to-end view of R&D productivity. In many companies, R&D functions are separated into distinct early-stage and late-stage organisations. A scenario could reasonably be imagined in which Company β's early-stage R&D organisation is considered to be high-performing, with solid early-stage success rates and consistent delivery of a high volume of molecules into the late-stage organisation, even though these subsequently suffer from high attrition later in development. In this scenario, the late-stage organisation may unfairly bear too much responsibility for its apparent below-average performance, when this may in fact be partly driven by high-volume and low-quality substrate delivery from the early-stage organisation.

To demonstrate the value of improving success rates in the real world, one of the factors underlying company J's high cost-per-output for 2017-2021 (Figure 4) was a relatively low success rate in Phase II. Improving this success rate to the median for the major company cohort would release USD1.3 bn from Company J's cost-per-approval figure (Figure 8). As outlined above, it would be important to ensure that changes made to achieve this do not adversely impact later-stage attrition.

Figure 8: Large reductions in cost per approval can be achieved even with modest improvements to underlying levers



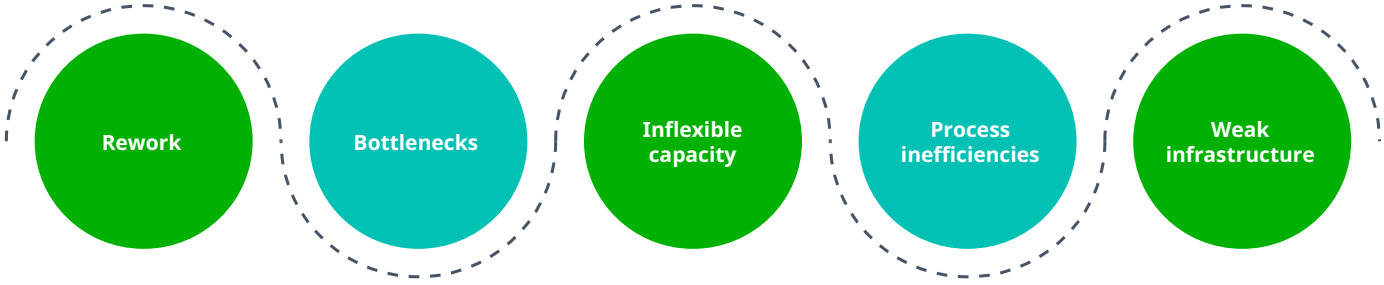
Source: IQVIA analysis.

Acting to improve productivity

The environment for clinical development has been increasingly challenging over the last decade impacting some of the key levers behind R&D productivity.[3] Some of the drivers behind this trend are increased clinical trial complexity; increased focus on chronic and degenerative diseases; difficulties in recruiting patients; a shift to complex modalities; and the need to conduct trials in emerging markets.

Choice of therapy area can mitigate some of these problems but, for most companies, there is a need to focus effort on some of the factors that typically cause delays and inefficiencies within the internal clinical development engine as illustrated in Figure 9.

Figure 9: Typical causes of delays in the development engine



Achieving the magnitude of improvements in underlying R&D levers that we have illustrated with the examples above is by no means unrealistic. Several companies in recent years have been able to demonstrate more dramatic improvements in success rates and cycle times than those we have described in our examples. Notably, these have typically resulted from systematic R&D performance initiatives conducted to address major historical R&D productivity issues, often at points of crisis. Broadly, we see a range of different approaches to optimising performance of the development engine some of which are shown in Figure 10, which illustrates cycle time based approaches.

Figure 10: Optimising R&D cycle times

Right first time	Optimized processes	Seamless transitions	Expedited decisions	Tech enablement
Avoid rework	**Remove inefficiencies**	**Avoid delays**	**Timely decision making**	**Tech levers for speed**
• Optimised protocol design • Patient centricity • Integrated evidence planning	• Integrated planning and resource management • Agile approach and mentality • Core enabling and differentiating processes optimised • Focus on peripheral processes such as contracting and payments	• Organisational transition points re-engineered to optimise speed • Outsourcing re-imagined as a strategic endeavour and optimised	• Re-definition of key decision points; criteria, accountabilities and responsibilities and supporting processes	• AI for patient and site identification • Data informed protocol design • Automation • Centralised control towers

Several companies have publicly reported impressive outcomes after identifying opportunities to improve productivity levers

Case study: Pfizer

In the early 2010s, Pfizer's R&D productivity lagged well behind that of its peers, with success rates – particularly in Phase II – a key 'brake' on performance at a time when the company was also facing a steep patent cliff. After conducting a systematic internal diagnostic, Pfizer took steps to increase its therapeutic area focus and expertise; reduce dependence on small molecules programs; increase the emphasis on target biology and proof-of-mechanism; increase the stringency of drug repurposing decisions; and improve portfolio governance.

Over a 10-year period, Pfizer's end-to-end success rate (from Phase I start to product approval) increased from 2% to around 20%, largely driven by an improvement in Phase II – which importantly did not happen at the expense of Phase III success rates.[7]

With respect to cycle times, Pfizer has also identified and targeted specific addressable components of clinical development duration, resulting in a cumulative improvement of over 2 years.[8]

Case study: Lilly

To address a major 2001 product patent expiry, Lilly redirected its resources to focus on development and commercialisation of several near-term launches, resulting in a problematic gap in its early-stage pipeline. Adding to the challenge, Lilly's Phase III success rate over the 2005–2010 period was extremely low, at 17% – which according to Lilly may have been driven by a paucity of high-quality early-stage substrate. Meanwhile, development speed was also below industry average.[9]

By the early 2010s, a new set of R&D governance and quality principles known as Timely Valued Medicines (TVM) had been established in an effort to systematically reshape the portfolio, focusing on fewer candidates but of higher quality, rather than a volume-driven approach to R&D.[9] Key aspects of TVM included: better understanding and validation of targets and disease opportunities; early tailoring to specific patient groups; identifying the best modalities for the opportunity; and increasing the data-driven rigour of pipeline progression decisions. The company also reduced its therapeutic area footprint to increase pipeline focus.[9,10]

By the 2014–2018 period, Lilly's Phase III success rate had increased dramatically, to 78%. In a similar timeframe, Lilly also reported a reduction of 2 years in its average development speed as a result of its 'Next Generation Development' initiative.[11,12] After subsequent targeting of research processes, Lilly now believes itself to be an industry leader in both preclinical and clinical cycle times.[13]

Case study: AstraZeneca

By the late 2000s, a series of pipeline failures at AstraZeneca had led to significant investment analyst concern around pipeline productivity. Over the 2005–2010 period, Phase II and Phase III success rates were both below industry average, whereas earlier-stage success rates tended to be above average, indicating a top-heavy attrition profile.[14] A systematic retrospective analysis of portfolio data and decision-making identified several critical factors associated with project fate, alongside a sub-optimal level of rigour in pipeline progression decisions.

To address these historical causes of low R&D productivity, AstraZeneca developed and implemented a '5R Framework', which defined a specific set of criteria against which projects would be rigorously assessed (Right Target; Right Tissue; Right Safety; Right Patient; Right Commercial Potential).

Implementation of the 5R framework had a dramatic impact on the performance and shape of the AstraZeneca Biopharmaceuticals portfolio. The overall success rate from candidate selection to Phase III completion increased from 4% (2005–2010) to 19% (2012–2016), with success rates improving in all component phases and with a reduced total pipeline volume through an emphasis on higher quality projects.[15]

Implementation of the 5R framework had a dramatic impact on the performance and shape of the AstraZeneca Biopharmaceuticals portfolio.

Beyond cost-per-approval

Although cost-per-approval is a major component of R&D productivity, there are other critical factors that we have not focused on here and which will be considered in future reports. The value of R&D outputs, typically measured in terms of NPV of the pipeline and/or of recent launches, or in terms of actual and/or forecast sales for new and emerging products, is also key in addition to their cost of delivery. Another important factor is business development, including licensing, divestments, mergers and acquisitions; this is obviously important for all major companies but may be especially critical for those companies where internal R&D productivity has been problematic.

Conclusions

Despite broadly increasing annual new drug approval volumes in recent years, R&D productivity varies significantly among individual major pharmaceutical companies. When measured in terms of cost-per-approval, R&D productivity can be significantly impacted by differences in cycle times and success rates, yet relatively modest improvements in fundamental performance levers can deliver substantially better outcomes. Such improvements are by no means limited to the hypothetical; several companies have been able to make dramatic improvements to productivity fundamentals contributing, at least in part, to huge improvements in company performance and in analyst perceptions of their respective R&D engines.

Unfortunately, large-scale systematic efforts to understand and subsequently to correct productivity fundamentals have typically only been triggered when companies have reached historical lows in terms of R&D productivity, leading analysts to question the value and sustainability of company pipelines over periods of several years.

We believe that there is a major opportunity for companies to conduct reviews of their R&D performance levers systematically and periodically in order to identify and proactively address areas for potential improvement before serious questions are already being asked by investment analysts and other external observers.

Cost-per-output modelling of the kind described in this paper can provide an important tool in a company's productivity toolkit, by enabling identification of key focus areas for further investigation and — where necessary — for productivity improvement work.

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