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## Supplementary information

# Efficiency, effectiveness and productivity in pharmaceutical R&D

In the format provided by the authors

**Scope**
Our analyses covered a cohort of pharmaceutical companies representing the top 14 by 2019 (pre-pandemic) R&D spending. These companies were: AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Gilead, GSK, Johnson & Johnson, Lilly, Merck & Co., Novartis, Pfizer, Roche, Sanofi and Takeda. All of these companies were still represented within the top 15 companies by R&D spend in 2022, with all but one also represented within the top 15 companies by sales.

**Historical and contemporary R&D performance analyses**
In examining a company's overall R&D performance, analysts often utilise macro-level approaches based on total R&D spending, product revenues and other company-reported financial metrics, considered over a lengthy historical timeframe. Although details vary, retrospective approaches such as these often introduce a lag time between the analysed R&D spending period and the analysed revenue period, in an effort to associate past R&D spending with a more recent cohort of product launches. Such analyses may also include estimated (R&D) business development spending, which can be highly significant — especially where mergers and other business acquisitions are concerned. Indeed, 'in-process R&D' components of infrequent but very large transactions will have a dramatic impact in retrospective analyses of this kind if they occur during the historical assessment period.

Although performance analyses based on historical financials are certainly useful, we believe they are of limited value in the specific context of assessing *contemporary* R&D performance. On an individual company basis, large organisational and strategic shifts in R&D are common, as are improvements and indeed declines in productivity. This limits the applicability of long-term retrospective analyses to current company performance.

In contrast, rather than providing a retrospective historical view, our 'snapshot' approach is intended to illuminate the *current* ability of company R&D engines to efficiently 'pull-through' investigational products and deliver value from the R&D pipeline. This is achieved by examining recent performance data for each of a series of fundamental productivity levers, across early- and late-stage R&D, before applying these data to calculate the cost and value of each new product approval at current levels of performance. With the goal of a current 'snapshot' view in mind, historical multi-year totals for R&D spend, business development spend, or product revenue are not required – nor is there a need to decide on an offset period of historical R&D expenditure to associate with a specific cohort of product approvals.

**R&D efficiency**
***Data*.** Across the 14 in-scope companies, our success rate and cycle time data for clinical development phases covered 1,516 projects distributed between 965 distinct assets from 2018–2022. These R&D data encompassed both in-house and externally originated assets (for example, those acquired through in-licensing, portfolio acquisitions or company mergers). Data concerning project fates and durations were derived and curated from two key information sources:

• AlphaSense (https://www.alpha-sense.com/): used to facilitate review of prior company financial filings, press releases and investor presentations for the analysis period.

• Pharmapremia (https://www.pharmapremiasolution.com/): Citeline database used for analysis of clinical development project outcomes.

Following a series of quality-control checks, project level outcomes were aggregated to the asset (investigational product) level, in order to facilitate comparison with analysts' commercial forecasts conducted at the product level. Between-phase success rates and between-phase cycle times were calculated for each company, at asset level, based on clinical-stage pipeline project outcomes.

Briefly, between phase success rates are calculated as the number of progressions to the next R&D phase divided by the sum of progressions and in-phase terminations. This is a standard, well-established approach to success rate calculations conducted by benchmarking organisations on behalf of pharmaceutical companies. Between-phase cycle times are calculated as the interval between the start of an R&D phase and the start of the subsequent phase. Cycle times therefore reflect a combination of factors including individual clinical study cycle times, the use of sequential versus parallel studies, decision-making time and other non-study considerations.

The range in company clinical-stage values across our cohort for both success rates and cycle times is shown below.

Success rates:
- Phase 1: 29%–53%
- Phase 2: 24%–67%
- Phase 3: 45%–89%
- Registration: 75%–100%

Cycle times:
- Phase 1: 1.8–4.1 years
- Phase 2: 2.0–4.7 years
- Phase 3: 1.4–5.9 years
- Registration: 0.6–1.5 years

For discovery and preclinical stages, cycle times and success rates were estimated using industry benchmark values cited in the literature[1]. The costs of success and failure for a single asset in each R&D phase ('cost-per-work-in-progress') were also estimated using industry benchmark values[1,2], adjusted to 2022 US dollars as shown in the table below:

**"Out-of-pocket" cost-per-work-in-progress by R&D stage (in 2022 US$ million)**

| Phase | Lead discovery | Lead optimization | Preclinical | Phase I | Phase II | Phase III | Registration |
|---|---|---|---|---|---|---|---|
| **Progressed** | 4.8 | 13.6 | 6.8 | 34.9 | 102.6 | 334.8 | 89.3 |
| **Terminated** | 4.8 | 13.6 | 6.8 | 28.2 | 58.6 | 183.2 | 48.9 |

Costs for discovery and preclinical stages were derived from Paul *et al.*[1], while costs from clinical development phases were derived from DiMasi *et al*.[2] The combined Phase III and Registration costs used by DiMasi *et al*. were apportioned into separate phases using the ratio of corresponding values from Paul *et al*.

***Methodology*.** Our cost per approval methodology was conducted broadly in line with the approach outlined by Paul *et al.*[1]. Company-specific, between-phase success rates (2018–2022) were used to back-calculate the number of assets required in each R&D phase in order to achieve a single regulatory approval at steady state, reflecting the impact of pipeline attrition. Asset successes and failures were then costed for each phase, using the 'cost-per-work-in-progress' benchmarks, adjusted for relative differences between progressed asset costs and terminated asset costs. In order to account for the time value of money, calculated 'out-of-pocket' costs for each R&D phase were capitalised using a representative discount rate of 8% up to the point of approval, from the midpoint of each R&D phase, using company-specific cycle times. The 8% cost of capital figure was selected as a representative value for the cohort following a review of annual financial filings.

The R&D efficiency metric therefore represented the average capitalised, attrition loaded cost of achieving a single new product approval for each company. The calculated R&D efficiency values are tabulated at the individual company level below.

**Company-level R&D efficiency (R&D cost per approval) values for 2018–2022 (inclusive)**

| Ranking in cohort | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| R&D cost per approval ($US billion) | 1.65 | 1.86 | 1.88 | 1.89 | 2.42 | 2.54 | 2.70 | 2.82 | 3.43 | 4.26 | 4.26 | 4.59 | 4.65 | 6.91 |

**R&D effectiveness**

***Data.*** Across the 14 companies in our cohort, 106 new product approvals were identified between 2018 and 2022, inclusive. For the purpose of our analyses, a new product was defined as a novel active ingredient or novel fixed-dose combination of active ingredients; as such, reformulations of previously approved active ingredients were excluded. The net present value (NPV) of each new product was estimated using analyst consensus forecasts. Data were derived and curated from the following sources:

• IQVIA Analytics Link (https://analyticslink.customerportal.iqvia.com): data were used for identification of launched assets and for derivation of consensus forecasts and NPV estimates.

• AlphaSense (https://www.alpha-sense.com/): used as a further source of reported forecasts to enable review and QC of NPV calculations.

• Regulatory agencies: agency websites were used as a further source of new product approvals and associated dates and sponsors at the point of approval. We examined approvals by the US Food and Drug Administration, the European Medicines Agency and the Ministry of Health Labour and Welfare of Japan.

We restricted our analyses to those products that received a first approval (US, EU or Japan) whilst in the hands of one or more cohort companies. Assets that were not held at the time of approval (e.g. if divested prior to approval or acquired post-approval) were not considered part of the dataset for that company. Externally acquired assets (e.g. those acquired through in-licensing, portfolio acquisitions or company mergers) were included only if — at the point of acquisition — they were still in R&D stage for their furthest-advanced indication.

***Methodology*.** Analyst consensus forecasts were derived for each new product approved between 2018-2022, inclusive. Revenue expectations were converted to NPV figures, after factoring-in estimates for cost of goods sold and selling, general and administrative expenses, alongside discounting from the point of approval. Average NPVs per new product approval were then calculated for each cohort company. Calculated R&D effectiveness values are tabulated at individual company level below.

**Company-level R&D effectiveness (NPV per approval) values for 2018-2022 (inclusive)**

| Ranking in cohort | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NPV per approval (US$ billion) | 20.4 | 18.0 | 14.7 | 9.6 | 7.5 | 6.0 | 5.9 | 4.9 | 3.5 | 2.9 | 2.6 | 2.4 | 2.4 | 2.4 |

**Productivity ratio**

***Data*.** An R&D productivity ratio was derived using the R&D efficiency and effectiveness metrics described above.

***Methodology*.** The R&D productivity ratio was calculated for each of the cohort companies by dividing the NPV per new product approval by the corresponding R&D cost per approval.

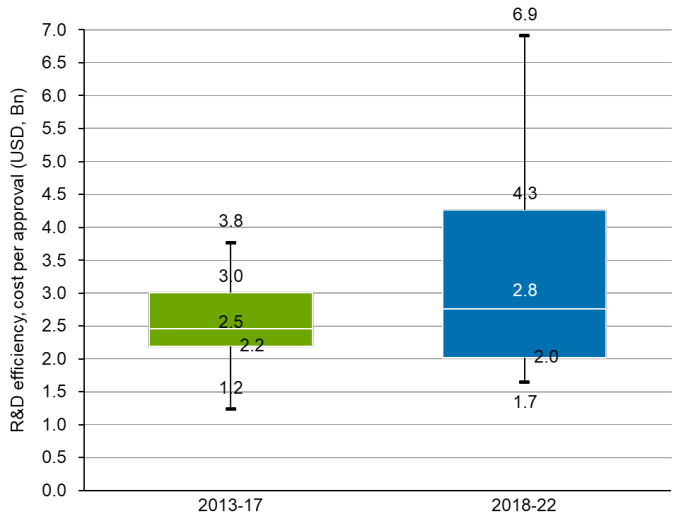
The cohort minima, mean, maxima and key percentiles for R&D efficiency (R&D cost per approval), R&D effectiveness (NPV per approval) and R&D productivity ratio (NPV per unit R&D cost) for 2018–2022 inclusive are provided in the table below:

**Summary productivity data for the cohort of 14 companies for 2018–2022 (inclusive)**

| | R&D cost per approval (US$ billions) | NPV per approval (US$ billions) | R&D productivity ratio (NPV per unit R&D cost) |
|---|---|---|---|
| **Mean** | 3.3 | 7.4 | 2.6 |
| **Median** | 2.8 | 5.4 | 2.2 |
| **Minimum** | 1.7 | 2.4 | 0.5 |
| **10$^{th}$ Percentile** | 1.9 | 2.4 | 0.6 |
| **25$^{th}$ Percentile** | 2.0 | 2.7 | 0.9 |
| **75$^{th}$ Percentile** | 4.3 | 9.1 | 3.0 |
| **90$^{th}$ Percentile** | 4.6 | 17.0 | 5.3 |
| **Maximum** | 6.9 | 20.4 | 8.0 |

**Changes in R&D efficiency over time**

Analysis of the changes in cohort level R&D efficiency from 2013–2017 to 2018–2022 reveals an apparent divergence in R&D efficiency. Whilst the cohort median for 2018–2022 was only slightly greater than that for 2013–2017, the spread of values — both at the extremities of the cohort and between quartiles — increased significantly. Although the majority of cohort companies remained largely stable between the two periods, a divergence in performance can be attributed to a number of sharp downturns and upswings within a few companies. Notably, additional analyses have indicated that the COVID-19 pandemic did not materially affect R&D efficiency for our cohort over a five-year analysis period.




**Supplementary Figure 1 | Changes in R&D efficiency (cost-per-approval) over time, comparing the most recent full five calendar years with the preceding five years.**

**Limitations**

Although company-specific data were used for success rates and cycle times in calculating R&D efficiency, individual asset 'costs-per-work-in-progress' within each phase were assumed to be equivalent across each company. Any unique operational efficiency factors within individual companies, whether positive or negative, may therefore be under-represented. In mitigation, prior literature[1] suggests that the impact of 'cost-per-work-in-progress' is less significant than the other R&D efficiency levers included in our analysis.

Publicly available data on cost-per-work-in-progress for discovery and preclinical projects are extremely limited, although pharmaceutical companies often have access to industry-level data through syndicated benchmarking programs in which they participate. In our analyses, we have used historical benchmarks cited in the literature, but anecdotal evidence indicates that these figures remain useful (when adjusted to 2022 dollars).

For R&D effectiveness, we used current 'snapshot' NPVs for new products (those first approved within the last 5 years), rather than NPV values at the point of first approval. As a result, historic prior sales do not contribute directly to product valuations, although they do of course serve to improve and refine forward-looking long-range revenue forecasts and thereby NPVs. In addition, NPVs were calculated for newly approved products based on analyst consensus forecasts, which may not always accurately reflect eventual real-world commercial performance. However, whilst consensus forecasts for individual assets can be inaccurate, the magnitude of discrepancy between forecast and actual revenues is greatly diminished at an aggregate level[3]. We therefore believe that the company-level average product valuations utilised in our analyses are appropriate and meaningful.

In comparison to the data utilised for R&D efficiency calculations, R&D effectiveness data are a somewhat 'lagging' indicator for R&D productivity, since meaningful forecasts are typically produced by investment analysts only as investigational products approach regulatory approval. Nonetheless, we believe that assessing effectiveness based on recent approvals, for which high-quality forecasts are available, is preferable to alternative approaches (relying on cruder forecasts for pipeline-stage assets, or on historical reported sales for older products).

We have not presented here any analyses assessing the influence of asset characteristics – such as modality, therapeutic area, orphan status, etc – on company R&D efficiency or effectiveness. As discussed elsewhere, the focus of the present analysis is to provide a current, snapshot view of company-by-company R&D productivity based on recent performance on a series of fundamental levers. Conducting meaningful calculations on this basis is dependent upon there being sufficient asset numbers, for each company, *in each R&D stage*. Although analysis of large asset subsets (e.g. oncology products) is viable, analysis of less-prevalent subsets requires either pooling of data across multiple companies (essentially providing an industry aggregate view) or significant expansion of the analysis timeframe (providing a more historical view) in order to achieve consistently high n-numbers. Since neither of these approaches are compatible with the present objective of providing a current snapshot view at individual company level, we have not provided any asset subgroup analyses in this article.

Finally, due to licensing/commercial limitations we are unable to disclose here individual company-specific values for cycle times and success rates, company-level R&D productivity ratios (including paired underlying efficiency/effectiveness data points), COGS/SG&A data, or individual products/NPVs included in R&D effectiveness calculations.

**References**

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