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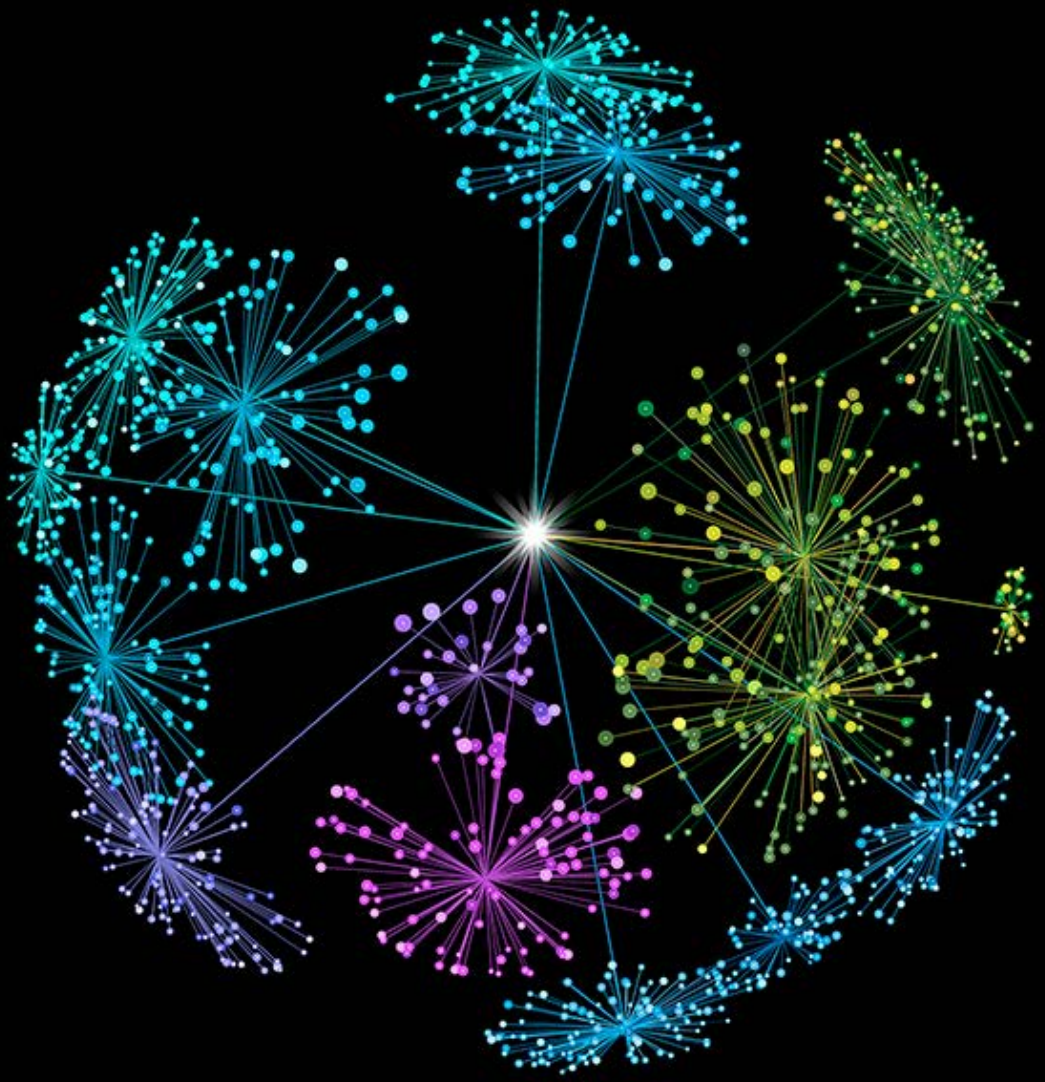


Seize the digital momentum

Measuring the return from pharmaceutical innovation 2022

January 2023

Deloitte Centre *for*
Health Solutions

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

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

In this publication, references to Deloitte are references to Deloitte LLP, the UK affiliate of Deloitte NSE LLP, a member firm of Deloitte Touche Tohmatsu Limited.

GlobalData is a global data & insights solution provider who, for over 40 years, has been helping over 4,000 companies worldwide to make more timely, fact-based decisions. Our mission is to help our clients succeed and be more innovative by decoding the future and reducing the noise & uncertainties surrounding the world of today. We do this by providing market data, competitive insights and end-user perspectives which are delivered to our clients in an integrated way through a variety of different tools.

Methodology

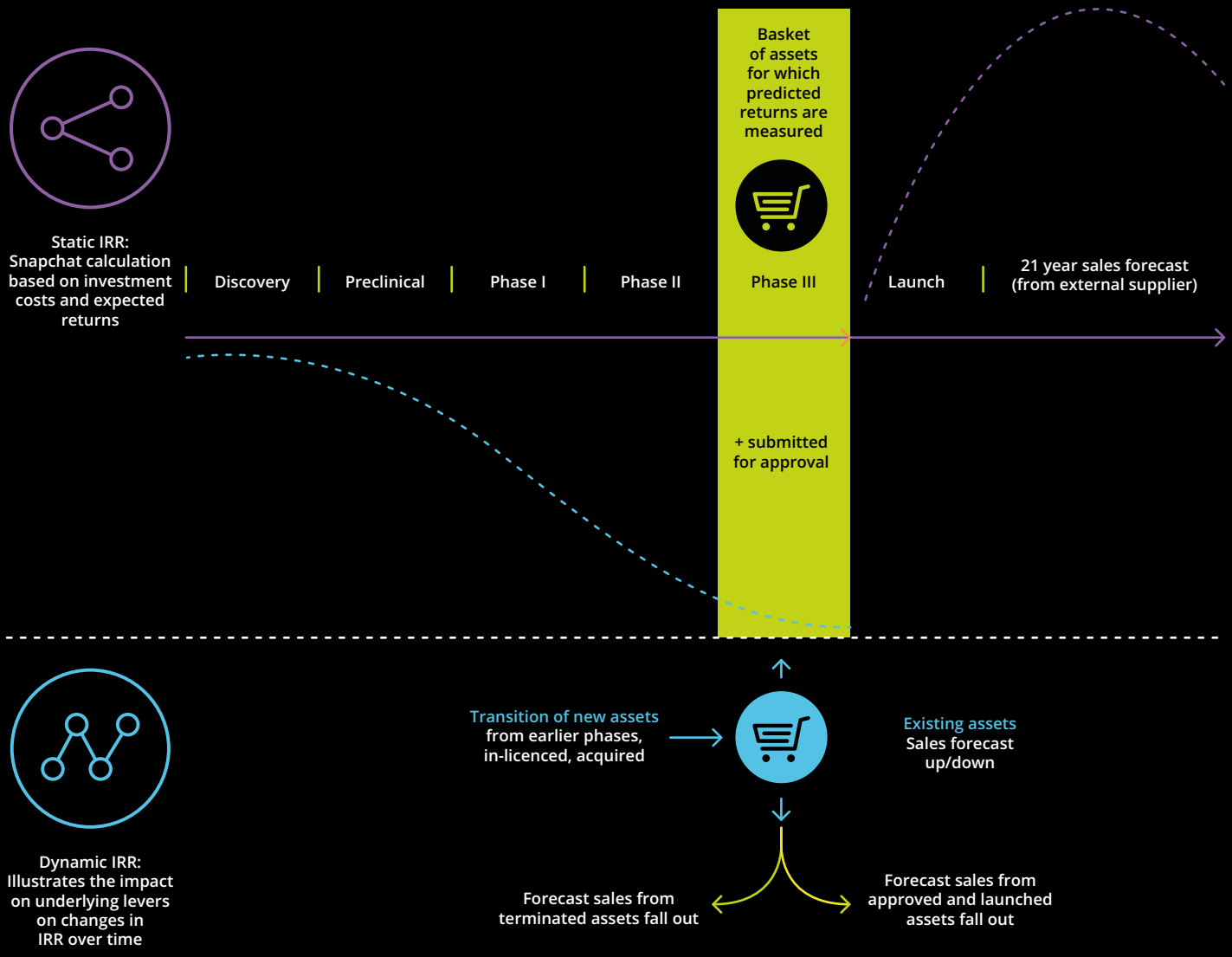
Underpinning our annual report Measuring the return from pharmaceutical innovation series is a bespoke Deloitte analytical model that calculates the Internal Rate of Return (IRR) that selected biopharma companies might expect to achieve from assets in their late-stage pipelines. These are assets that are expected to launch within the next one to four years (filed, in Phase III or Phase II with breakthrough therapy designation as of 30th April each year). We use this analysis of IRR to act as a proxy measure of the industry's ability to balance initial capital outlay on R&D with the cash inflows that the companies are projected to receive from their investment in innovation. The data we used to populate the model is from publicly available, audited annual reports and sales forecasts provided by GlobalData. This document explains the research methodology.

Measuring projected returns is extremely complex and therefore imperfect, the analysis that underpins our series of annual reports provides a consistent and objective methodology to assess performance. In turn this allows us to derive insights into opportunities for improving return on investment in R&D. The underlying principles are comparability (a consistent, unbiased, direct comparison across the industry and investments of different sizes), accessibility (relevant to a diverse audience, both within and outside of the biopharma industry) and availability (the analysis is derived from public information available from audited annual reports or readily accessible from third-party data providers).

As assets are approved (launched) their forecast revenues move from the late-stage pipeline into the commercial portfolio, moving out of scope of our analysis. Figure 1 provides a high-level overview of the methodology for calculating both a static year-on-year return and a dynamic (three-year rolling average) measure of R&D returns.

Figure 1. Late-stage pipeline static IRR and drivers of change in IRR methodology

Late-stage pipeline static IRR and drivers of change in IRR methodology



Source: Deloitte LLP, 2022 .

Original cohort

Since 2010, we have analysed the performance of a cohort termed 'original cohort' which comprises the top 12 publicly listed, research-based, life science companies measured by 2008-09 R&D spend, namely: Amgen, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck & Co., Novartis, Pfizer, Roche, Sanofi, and Takeda.

Extension cohort

In 2015, we introduced an extension cohort of four companies (AbbVie, Biogen, Celgene, and Gilead), selected based on their performance and pharmaceutical R&D spend. All fell within the top 25 pharmaceutical companies based on R&D spend for 2012 to 2014. The analysis of the extension cohort was retrospectively calculated to 2013. In 2020, Bristol-Myers Squibb's acquired Celgene and consequently the extension cohort was reduced to three companies.

Combined cohort

In 2020, after seeing a convergence in the performance of our original and extension cohorts, we merged the two cohorts into a 'combined cohort' and focused our analysis on the aggregate performance of the combined cohort.

Top 20 R&D cohort

Since 2020 we have also analysed an additional five companies (Astellas, Bayer, Boehringer Ingelheim, Novo Nordisk and Regeneron). This expands our analysis to cover the top 20 biopharma companies by R&D spend.

Assets evaluated

As noted, our analysis focuses on each company's late-stage pipeline defined as the set of assets that are filed, in Phase III or Phase II with breakthrough therapy designation as of 30th April for each relevant year. The types of assets included are:

- New Chemical Entities (NCEs)
- New Biological Entities (NBEs)
- significant line extensions expected to result in a measurable uplift in revenues
- reformulations
- fixed dose combinations
- biosimilars.

For all assets included in the analysis, their origin was assessed, and they were categorised as self-originated, in-licensed, out-licensed, part of a joint venture/co-development or acquired.

Methodology amendments & restatements of prior-year results

We are continually working to improve the methodology and modelling that underpins this report. Due to the complex nature of the analysis and despite rigorous quality review procedures minor errors are occasionally identified in previously published data.

Any methodology amendments are adjusted for retrospectively but applied consistently, allowing year-on-year comparison of trends. Where amendments are identified, we assess the materiality based on the impact this has on IRR.

Judgement is then applied to determine whether to amend results retrospectively. No adjustment is made where new information subsequently becomes available which was not available at the time of performing the analysis, for example, incorporation of actual sales data or restatement of figures published in company annual reports.

Principles applied to the model

Currency

All currency calculations have been made in US dollars. Yearly average rates have been used for conversion of other currencies into US dollars.

Taxation

IRR has been calculated based on post tax inflows and outflows. Company specific tax rates have been calculated based on average effective tax rates over the ten years preceding the year of the report, adjusted for non-recurring items, such as litigation costs, impairments, and in-process R&D (IPR&D) expense.

Yearly static returns

Static returns are calculated for a defined basket of late-stage assets by estimating the expenses associated with developing the assets and the likely potential returns that they will deliver, equating cash outflows with cash inflows to generate an IRR value. A separate IRR value is generated for each year of the report based on each company's:

- annual R&D expenses (cash outflows) for the prior ten years – which calculates the cost associated with bringing the basket of assets to a particular stage of development (using data from publicly available, audited annual reports).

- annual risk-adjusted revenues (cash inflows) forecast for the future 21 years – which estimates the likely returns that the basket of assets is projected to deliver (revenue forecasts provided by GlobalData).

Average returns

Average returns are calculated on a weighted three-year rolling average basis by aligning the individual inflows and outflows used in the static returns figure for the three periods included in the rolling average.

Dynamic returns

Calculating dynamic returns allows the movement in static returns from one year to the next to be reconciled and quantifies the key elements driving this change. It is calculated to bridge each time-period, as well as the overall time from 2010, and focuses on the same basket of late-stage pipeline assets as the static returns. However, the basket of assets changes year-on-year due to the movement of assets into and out of the late-stage pipeline.

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

Cash outflow elements

The four outflow elements driving change in IRR comprise:

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

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

Cash inflow elements

The inflow elements driving change in IRR comprise:

- Forecast revenues, which can be split into:
- terminated – loss of forecast revenues from late-stage pipeline due to termination of assets
- approved – transfer of forecast revenues to the commercial portfolio as assets launch and therefore leave the late-stage pipeline
- existing – increases or decreases in forecast revenues for assets which remain within the late-stage pipeline
- new – forecast revenues associated with new assets entering the late-stage pipeline
- changes in a company's average cash operating margin.

The annual impact of each factor on the cash inflow has been analysed in isolation so that their individual impact on returns can be quantified.

Model inputs: R&D cash outflows

Cash outflows were calculated separately for self-originated, in-licensed and acquired assets.

Self-originated assets

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 identified through profit and loss accounts are assumed to equal cash flows, unless a non-cash expense is separately disclosed (e.g., write-off of 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 limits the model to the use of industry average cycle times and cost allocation when calculating R&D costs over the ten-year period; Deloitte and GlobalData proprietary data was used for 2022 (see Figure 2). This methodology incorporates the cost of failure or asset attrition from the cohort at discovery to the late-stage pipeline as of 1 January for each respective year (using data from publicly available, audited annual reports).

5. R&D costs have not been included within the model beyond the most recent year end for each of the companies in question.

Figure 2. Industry average benchmarks 2022

Industry average benchmarks	R&D cost allocation	R&D cycle times
Discovery to first toxicity dose	24%	33%
Preclinical to Phase II	28%	43%
Phase III and submission	49%	24%

Source: Deloitte and GlobalData proprietary data

Assets acquired through in-licencing

For assets which have been in-licensed from a third party, any upfront payments have been included in the relevant year of acquisition. In-licensing information was provided by GlobalData. In most cases financial information was limited due to the commercial sensitivity of deal information. 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 assets have been assumed to be incurred at their maximum potential amounts on commencement of sales of the assets. Any costs expended in developing the product after in-licensing have been included as per the internally developed assets.

Where deal values have not been disclosed, industry averages by therapy area have been utilised as a proxy for the costs of acquiring IP. Industry average royalty rates per stage of development at the time of deal formation have also been utilised.

For deals involving a basket of assets, deal values have been weighted according to the number of assets for deals done in early-stage, or, for late-stage deals where lifetime sales forecasts are available, weighted according to the revenue contribution from the individual constituents of the deal.

Assets acquired as part of a business combination

The method applied to account for R&D costs incurred as part of a business acquisition varies based on materiality of the transaction to the calculation of IRR.

1. R&D costs incurred after the date of the business acquisition have been included as per the internally developed assets noted above.

2. Where the acquired company has reasonably stable historic R&D spend, stable historic operating margins (i.e., has a significant commercial portfolio) and is considered of a material size, a full consolidation approach is taken. This means R&D costs prior to the date of acquisition have been included separately in the model based on publicly available annual reports and applicable GAAP at the time results were issued (either local GAAP applicable in the country of incorporation, IFRS or US GAAP).

3. Where acquired companies did not meet the definition above, acquired in-process R&D figures are taken as the figure paid for the R&D portfolio. This separates the value of the R&D pipeline from any commercial portfolio acquired or net value of the company's assets less liabilities.

The costs associated with assets acquired as part of a business acquisition have not been included independently as these are captured via the inclusion of the acquired company's pre-acquisition R&D cost or IPR&D. Further, publicly available data does not typically include the fair value attributed to each of the assets acquired. Any costs expended in developing the product after the business acquisition have been included as per the internally developed assets.

Model inputs: Forecast cash inflows

Sales forecasts

1. Asset sales were forecast for a 21-year timeframe for each period under investigation.

2. 2022 revenue forecasts were calculated by GlobalData using a combination of forecasting methodologies, including analyst consensus forecasts and proprietary patient-based forecasting models to generate revenues to 2042.

3. Revenue forecasts have been risk-adjusted for Phase III and submission success rates specific to therapeutic areas (GlobalData proprietary data).

4. Sales forecasts were determined in July of the report year; forecasted revenues are based on knowledge and events as of this date.

5. After reaching peak sales, standard erosion curves were applied depending on the type of asset considered. Different erosion curves have been developed for each asset type: small molecules (chemical entities) and large molecules (biological entities).

6. Available patent information was extracted by GlobalData from GlobalData's Pharma eTrack and other public patent sources for each asset. Accurate patent data can be difficult to locate, therefore, several rules were defined to ensure consistency across the assets.

Margin applied to sales forecasts

Inflows have been determined by applying an average un-leveraged cash-flow adjusted operating margin. This has been calculated using operating profits reported in publicly available company reports over the three-years preceding each year.

Modelling assumptions

The use of forecast data and publicly available information regarding pipelines and deal information presents certain challenges and risks. These challenges and risks include, but are not limited to, the following:

1. The late-stage pipeline considered for our analysis is based on all public information available as of 30th April in the year of the report. There is often a lag in obtaining intelligence on product launches, particularly of line extension products, and intelligence on new Phase III compounds entering the late-stage pipeline. This may mean products are removed from the pipeline the year following launch or may have a delay in pipeline inclusion until the year following Phase III entry.

2. Deal and licensing information is commercially sensitive and therefore exact financial information is limited. During the research phase several proprietary databases combined with publicly available information have been used to construct a picture of the costs associated with compounds. It is important to note however that not all in-licensing and deal financial information is available outside of the companies involved, therefore some deal information used within this study does not have financial values associated with it.

3. The revenue and portfolio information provided in this 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 statements are based on reasonable assumptions listed here, any forward-looking statements by their very nature, involve risks and uncertainties. These forward-looking statements may be influenced by factors which affect actual outcomes or results to be materially different from those predicted here.

4. All forward-looking statements reflect knowledge and information available as of 30th April and are not updated post publication.

5. In-licensing costs included in the model are limited to those products included in the late-stage pipeline, thus in-licensing costs associated with compounds that failed prior to Phase III are not included.

6. The use of publicly available data limited the model to the use of industry average cycle times and cost allocation when calculating R&D costs over each 10-year period. This prevents an assessment of differences in development performance between each organisation, for example, therapeutic area and development programme specific cycle times are ignored and companies with better than average cycle times are not rewarded in this model.

7. Historic R&D costs have not been included within the model beyond the most recent year-end for each company.

8. The assumption that average cash operating profits over the three-year historical time period reflect future margins over the 21-year revenue forecast period may fail to fully reflect the impact of recent corporate cost reduction initiatives where relevant.

9. Revenue forecasts have been risk-adjusted using historical Phase III and submission success rates that may not model potential future changes in the regulatory and payer environment.

10. The model is sensitive to the distribution of compounds across the late-stage pipeline (Phase III to submission) and as this drives cash flow timing, a snapshot taken in a different year could generate different results.

11. Important factors that could cause results to differ materially from those contained in forward-looking statements, some of which are beyond our control, include:

- the loss or expiration of patents, marketing exclusivity or trademarks
- the risk of substantial adverse litigation/ government investigation claims and insufficient insurance coverage
- exchange rate fluctuations
- the risk that R&D will not yield new products that achieve commercial success
- the risk that strategic alliances will be unsuccessful
- the impact of competition, price controls and price reductions
- taxation risks
- the risk of substantial product liability claims
- the impact of any failure by third parties to supply materials or services; the risk of failure to manage a crisis
- the risk of delay to new product launches
- the difficulties of obtaining and maintaining regulatory approvals for products
- the risk of failure to observe ongoing regulatory oversight
- the risk that new products do not perform as expected
- the risk of environmental liabilities
- the risks associated with conducting business in emerging markets
- the risk of reputational damage
- the risk of product counterfeiting.

Nothing in the report or analysis should be construed as a profit forecast.

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