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New perspectives for better R&D performance: lessons learned from leading pharma companies

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The research and development (R&D) productivity of pharmaceutical companies has been widely studied and analyzed for many years in both academia and industry, and pharmaceutical companies have launched various initiatives to improve their R&D efficiency, such as by opening R&D toward external innovation, improved decision-making, or better clinical trial management. However, these efforts are based primarily on an inward-looking organizational perspective and have so far not benchmarked new drugs invented internally and those acquired from external sources. Here, we analyze new drugs approved between 2011 and 2022 developed by the top 20 pharmaceutical companies, differentiating between internal and external innovation, with a particular focus on internally invented new drugs. Based on our analysis, we provide deep insights into the R&D strategies of the leading companies and draw conclusions about how companies could further improve their R&D performance.

Keywords: Pharma; R&D; R&D productivity; open innovation; drug discovery; biotech; big pharma

FEATURE

Introduction

'R&D strategy' is a term that is not well defined in the scientific literature.[(p1),(p2)] With respect to the pharmaceutical industry, it can be understood as a framework that guides the direction of an R&D organization. It defines both the technological capabilities that a company needs for R&D competitiveness as well as decision-making in the dynamic and complex field of biomedical sciences and new drug development. This forward-looking perspective on strategy, understood as goals for which a firm is striving,[(p3)] is contrasted in the academic literature by Mintzberg's definition of strategy, which conceptualizes it retrospectively as the sum of the past decisions of a firm.[(p4)] In this sense, we define R&D strategy as the cumulative set of past decisions and resource allocations in R&D, including R&D expenditure, the selection of drug targets, the therapeutic areas pursued in drug discovery, or the therapeutic areas targeted by acquired assets.

R&D strategies of the leading pharmaceutical companies evolved over time, particularly in response to the increasingly important R&D productivity challenge, described in the literature since the 1960s.[(p5)] When the term 'productivity crisis' was first introduced, it became evident that R&D productivity is a highly relevant issue for the industry and not only an academically interesting topic.[(p6),(p7),(p8),(p9)] In response, numerous pharmaceutical companies started initiatives aimed at improving the efficiency of their R&D organizations. For instance, AstraZeneca,[(p10),(p11)] Eli Lilly,[(p12)] Boehringer Ingelheim,[(p13)] Pfizer,[(p14)] and Bristol-Myers Squibb (BMS) aimed to improve their R&D performance by leveraging external cost-efficient R&D,[(p15)] opening R&D toward more external innovation,

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improving preclinical decision-making, or adjusting clinical trial management. For instance, several leading firms tried to leverage the potential of open innovation by restructuring their R&D organizations in ways that facilitate the integration of new scientific knowledge, emerging technologies, novel drug targets, and externally invented drug candidates.[p16,p17,p18,p19] This also comprises activities in open science, such as Boehringer Ingelheim's opnMe.com,[p20] the formation of partnerships and strategic alliances,[p21] and as the licensing and acquisition of external drug candidates.[p22]

The trend toward external innovation is mainly driven by the intention to: (i) reduce dependence on internal R&D; (ii) react to technological trends; or (iii) fill crucial capability gaps when companies lack competitive advantage.[p23] Access to more external innovation should increase R&D output, enhance the innovativeness of the companies, defined as the ability of a firm to sustainably develop new drugs,[p24] thereby ultimately increasing R&D productivity.

In this context, we analyzed publicly available information relating to the 20 leading pharmaceutical companies and asked how these companies performed in terms of their R&D activities in recent years.

Analysis concept

We used a mixed-methods approach, primarily descriptive quantitative analyses complemented by descriptive qualitative elements. The analyses were conducted at the level of the R&D organizations of the 20 leading pharmaceutical companies (by total revenues 2022),[p25] rather than at the project or team level. We analyzed R&D input, R&D output [the number and quality of new US Food and Drug Administration (FDA)-approved drugs], and R&D outcome (revenues generated by these new drugs).[p7,p26]

We analyzed R&D performance of these 20 R&D organizations based on publicly available information relating to R&D and innovation. In this context, R&D performance was defined as a measure of how efficiently and effectively an R&D organization achieves its intended output or outcome.[p7,p27] Innovation was defined both as a process (i.e. activities to develop innovation) as well as an outcome, such as new products.[p24] As outlined previously,[p28,p29] the FDA defines innovation as an outcome, specifically as a new drug, when approved by its Center for Drug Evaluation Research (CDER). The quality of such innovations can vary, based on factors such as novelty or differentiation from existing treatments. For instance, first-in-class drugs, despite ongoing debates about their therapeutic value,[p29] are regarded as major scientific advances and examples of pharmaceutical innovation that have the potential to address unmet patient needs.[p29,p30] Similarly, the FDA links innovation to its approval processes. Although drug candidates approved through the standard review process are generally regarded as representing standard innovations/improvements (incremental innovations),[p31] a priority review designation is granted to drugs demonstrating clear differentiation and major therapeutic improvements or treatments for indications with no existing therapy (radical innovation).[p31,p32,p33]

To investigate this, we collected data from 2011 to 2022 on 237 new drugs, including new molecular entities (NMEs, small-molecule drugs) and new therapeutic biologics (NTBs), approved by the FDA's CDER, along with the corresponding patent and commercial information. For each new drug, information on the drug target, approval process, and therapeutic modality was analyzed. New drug data, such as brand name, international nonproprietary name (INN), sponsor, mechanism of action, therapeutic indication, and review path, were taken from the official FDA website. Additional information, such as drug target, was derived from DrugBank (https://go.drugbank.com/).

Basic patents claiming the active ingredient were identified by information from FDA Orange Book (https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm) or with help of the Canadian Patent Register for Drugs & Health Products (https://pr-rdb.hc-sc.gc.ca/pr-rdb/index-eng.jsp). In a few cases, the basic patents had to be identified using Google Patent and Drug Bank. In all cases, the US patent documents were reviewed via Espacenet (https://worldwide.espacenet.com/), and the relevant patent information [patent family, filing date, applicant(s), proprietor(s), an inventor(s)] was retrieved.

Based on information of the original applicant, the new drugs were segmented into three source categories: (i) internal, that is, assignee (entity that filed the patent) and sponsor (entity that received FDA approval) are part of the same pharmaceutical company; (ii) external, that is, assignee and sponsor are not part of the same legal entity; (iii) collaborative, that is, there is more than one assignee and one of those is the sponsor. This information was used to determine the origin of innovation.[p32,p33]

The classification of the origin of innovation from a business model perspective was conducted on a purely qualitative-descriptive basis. Data on new approved drugs as well as the source categories of the active ingredient were used as the basis for a segmentation into four categories: 'internal'; 'external'; 'multi-sourced'; and 'hybrid' R&D models. For these four categories, no quantitative definitions exist. Rather, these categories should be understood as illustrative descriptions of where companies stand in their R&D models from an open innovation perspective. In this context, 'internal' is defined as predominantly internal, 'external' as predominantly external, and 'multi-sourced' is distinguished from 'hybrid' in that, in the multi-source category, companies utilize multiple different sources of innovation, whereas in the hybrid category, the model emerges from two dominant innovation sources.

Commercial data for each drug (i.e. global revenue per year after FDA approval), were compiled from annual and quarterly company reports. All amounts in foreign currencies were standardized with historic, average US$ exchange rates retrieved from the Federal Reserve (https://www.federalreserve.gov/datadownload) and adjusted for inflation (indexed to 2022). The commercialization time was calculated as follows: years from new drug approval by the FDA till 2022 (last year of our analysis) or, in the case of post-approval acquisitions, years from acquisition until 2022.

In the case of Astellas, Daiichi Sankyo, and Takeda, the financial year (FY) ends on March 31 of the subsequent year,

which does not fully align with the calendar year. Given that most of the FY falls within the stated calendar year, the reported revenues were manually adjusted using a calendarization approach to ensure consistency with the calendar year.

Furthermore, in some cases, companies did not report the revenues of individual drugs separately but grouped them together, such as under 'all other [name of therapy area] revenues'. In this analysis, unreported revenues of drugs were set to zero, because their grouped nature suggested they are immaterial and not significant enough to impact the overall results.

R&D performance of leading pharmaceutical companies

We analyzed and benchmarked the R&D performance of 20 leading pharmaceutical companies between 2011 and 2022 using three key dimensions: (i) R&D output, measured by the number of new FDA-approved drugs; (ii) innovation quality, assessed through the ratio of first-in-class drugs and approval pathways; and (iii) R&D outcome, evaluated by the commercial success of innovations, indicated by new drug sales (Table 1).

Between 2011 and 2022, the 20 companies invested a total of US$1546.8 bn in R&D, corresponding to an average R&D intensity of 18%. During this period, the leading companies launched a total of 237 new drugs, which together generated sales of US$1322.8 bn, with an average commercialization time per drug of 6.5 years. The R&D output and outcome of the companies analyzed varied significantly. For instance, R&D output ranged from Novartis (24 new drugs) to Daiichi Sankyo (3) and Novo Nordisk (3). With regard to R&D outcome, the scope ranged from Gilead Sciences (US$163.5 bn) to Daiichi (US$12.1 bn). Looking at the new sales ratio, that is, the share of total sales generated by newly approved drugs, Gilead Science (53%) and BMS (43%) performed particularly well, indicating the strengths of their innovation pipelines, whereas Sanofi reached a ratio of only 4% with their new drugs.

The 237 new drugs can be split into 158 NMEs (67%), 77 NTBs (32%), and two other modalities (1%). Pfizer (94%), AbbVie (90%), Novartis (88%), and Merck & Co. (81%) had a very high share of NMEs among the newly approved drugs. Only Sanofi (67%), Novo Nordisk (67%), Biogen (60%), and Roche (59%) had a disproportionately high share of NTBs in their new drug portfolios. Of the 237 new drugs: 96 (41%) were approved by the standard review process, 141 (59%) were granted priority review designations, and 96 (41%) were first-in-class drugs. On a firm-level, Roche (88%), Bayer (88%), and Gilead (80%) had a disproportionately high number of priority review designations of their new drugs. By contrast, all three of Novo Nordisk's new drugs were approved through the standard review process. In terms of first-in-class drugs, BMS excelled with ten first-in-class approvals, accounting for 67% of its total new drugs, whereas Novo Nordisk did not launch a first-in-class drug between 2011 and 2022.

Origin of innovation and business models in R&D

We analyzed the origin of innovation of the newly approved drugs to gain deeper insights into R&D strategies, particularly in relation to drug discovery. The active ingredients of 86 new drugs (36%) were invented internally, 19 (8%) were co-invented with an external partner, and 132 (56%) were invented externally (Figure 1), reflecting R&D strategies that focus on both internal and external innovation. Broken further down into the therapeutic modalities, most internally invented (69%), acquired (63%), and collaboratively invented new drugs (85%) were small molecules (Table 1). With regard to approval process, internally invented drugs showed an almost equal ratio of standard (48%) and priority review (52%) designations. The share of drugs approved via the priority review process was higher among externally acquired drugs (60%). Collaboratively developed new drugs showed the highest proportion of priority review designation (90%). In terms of first-in-class and non-first-in-class drugs, no significant differences were observed across the different origins of innovation (Table 1).

At a firm-specific level (Table 2), Sanofi (83% externally invented new drugs) and Takeda (86%) relied primarily on external origins of their innovations. Most other companies leverage both internally and externally invented new drugs, whereas Bayer (75%), Boehringer Ingelheim (100%), and Novo Nordisk (100%) had a strong focus of their R&D strategies on internal drug discovery. Although also focused on internal drug discovery, Gilead had a unique positioning, with one (10%) externally, three (30%) internally and six (60%) collaboratively discovered new drugs.

To better understand the focus of internal drug discovery, the internally invented new drugs were analyzed in more detail (Table 2). Boehringer Ingelheim (71% of internally invented drugs), Pfizer (89%), Novartis (91%), AbbVie (100%), Bayer (100%), Gilead (100%), and Merck & Co. (100%) relied strongly on internal small molecule-based drug discovery, because most new drugs are NMEs. By contrast, Johnson & Johnson (67%), Novo Nordisk (67%), and Roche (83%) demonstrated a notably high share of NTBs among their fully internally developed new drugs.

Another insight from the R&D strategies emerges from the therapeutic areas and drug target classes of the new drugs (Tables 1 and 2). First, the number of therapeutic areas in which companies successfully invented new drugs internally averaged 2.8 (median: 3.0), which was lower than the overall average of 4.7 therapeutic areas (median: 5.5) in which companies obtained new drug approvals between 2011 and 2022. Second, a similar pattern was observed for the drug target classes investigated by the companies: internal drug discovery covered an average of 2.7 drug target classes (median: 3), whereas total R&D activities covered an average 4.2 drug target classes (median: 4.0).

We also analyzed whether the origin of innovation had any association with commercial aspects. First, internally invented new drugs generated average annual revenues of US$905 mn (Figure 1). Collaboratively invented new drugs showed a mean annual revenue of US$1034 mn. By contrast, externally invented and acquired new drugs generated mean annual revenues of US$579 mn.

Examining the various origins of innovation from a business model perspective, four distinct patterns could be qualitatively described (Figure 2): (i) 'internal R&D' model, exemplified by Bayer, Boehringer Ingelheim, Novo Nordisk, and Gilead Sciences, which primarily relies on internal drug discovery, either through

TABLE 1

R&D performance of leading pharmaceutical companies (2011–2022)[a]

Company	Total revenues (US$bn)	Total R&D spending (US$bn)	R&D intensity (%)	New drugs	New drug sales (US$bn)	New sales ratio	Avg. comm. time (y)	No. of NMEs	No. of NTBs	Other modalities	Standard review process	Priority review process	FIC drugs	No. of target classes	No. of therapeutic areas
AbbVie	430.6	71.1	17%	10	74.8	17%	5.0	9	1	0	5	5	4	4	5
Amgen	307.2	55.8	18%	8	23.5	8%	6.0	4	4	0	5	3	5	4	5
Astellas	161.7	29.0	18%	4	14.5	9%	7.0	3	1	0	1	3	2	3	3
AstraZeneca	394.8	88.4	22%	20	86.7	22%	6.2	10	10	0	9	11	7	6	8
Bayer	362.3	45.8	13%	8	18.6	5%	7.0	8	0	0	1	7	2	4	4
Biogen	144.1	29.8	21%	5	52.0	36%	7.0	1	3	1	3	2	3	3	1
Boehringer Ingelheim	318.4	54.2	17%	7	50.0	16%	8.0	5	2	0	4	3	4	5	4
Bristol-Myers Squibb	356.7	88.2	25%	15	152.0	43%	6.5	9	6	0	6	9	10	5	6
Daiichi Sankyo	135.7	28.7	21%	3	12.1	9%	5.3	2	1	0	1	2	1	2	2
Eli Lilly	322.5	77.8	24%	12	62.7	19%	5.6	6	6	0	7	5	3	3	6
Gilead Sciences	309.6	48.8	16%	10	163.5	53%	6.9	10	0	0	2	8	4	3	2
GlaxoSmithKline	547.6	84.4	15%	16	50.5	9%	8.0	10	6	0	8	8	5	6	6
Johnson & Johnson	713.7	117.6	16%	16	100.2	14%	7.3	11	5	0	6	10	7	5	6
Merck & Co.	631.4	136.3	22%	16	100.1	16%	6.8	13	3	0	6	10	8	5	6
Novartis	733.0	129.6	18%	24	52.9	7%	5.7	21	3	0	8	16	9	5	6
Novo Nordisk	242.3	32.1	13%	3	29.9	12%	5.3	1	2	0	3	0	0	3	1
Pfizer	826.1	118.5	14%	17	75.3	9%	6.8	16	1	0	8	9	5	5	6
Roche	816.6	168.9	21%	17	123.2	15%	6.7	7	10	0	2	15	9	4	5
Sanofi	615.3	90.4	15%	12	25.4	4%	6.2	3	8	1	5	7	5	5	6
Takeda	295.7	51.5	17%	14	54.9	19%	7.0	9	5	0	6	8	4	4	6
Total	8665.3	1546.8		237	1322.8	–	–	158	77	2	96	141	97	–	–
Average	433.3	77.3	18%	11.9	66.1	17%	6,5	7.9	3.9		4.8	7.1	4.9	4.2	4.7
Median	359.5	74.5	18%	12.0	53.9	15%	6.8	8.5	3.0	0	5.0	7.5	4.5	4.0	5.5

[a] R&D input, output, and outcome of top-20 pharmaceutical companies (2011–2022) broken down as total R&D spending, R&D intensity, number of new FDA approved drugs, sales (US$bn) generated by new drugs, new sales ratio, and average commercialization time (years). New drugs are further subcategorized as number of NMEs, number of NTBs, number of new drugs with other modalities (other than NME or NTB), number of drugs approved by standard review, number of new drugs granted priority review designation, number of FIC drugs, number of drug target classes, and number of therapeutic areas.

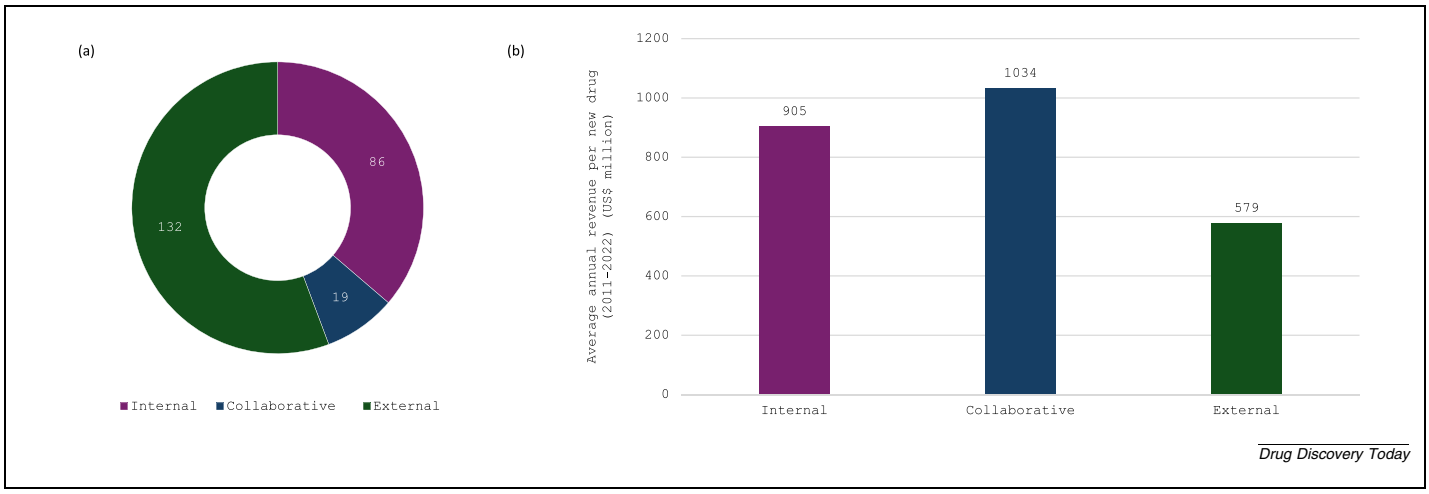

FIGURE 1

Locus of innovation of new drugs approved by the US Food and Drug Administration (FDA) for leading pharmaceutical companies (2011–2022). **(a)** Number of new drugs by locus of innovation: (i) internally invented (internal, pink), collaboratively invented (collaborative, blue), and externally invented and acquired (external, green). **(b)** Commercial performance (average annual revenue in US$million) per new drug split by locus of innovation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in-house or collaborative efforts; (ii) 'external R&D' model, exemplified by Takeda and Sanofi, with a strong focus on externally invented new drugs; (iii) 'hybrid R&D' model, exemplified by Novartis, Roche, Pfizer, Eli Lilly, Biogen, and Daiichi Sankyo, in which internal and external innovation are well balanced; and (vi) 'multi-sourced R&D' model, exemplified by AstraZeneca, GlaxoSmithKline, Merck & Co., Johnson & Johnson, BMS, AbbVie, Amgen, and Astellas, which represents a more diversified R&D strategy compared with the 'hybrid R&D' model, because new drugs are sourced through various sources.

Limitations

Measuring R&D performance is complex and context dependent[(p34)]. Accordingly, we acknowledge that this analysis captures only selected aspects of the overall performance of the R&D organizations and, therefore, is not fully generalizable.

Using a quantitative descriptive methodology based on publicly available data, R&D performance can only be assessed in segments or specific dimensions. A comprehensive evaluation, including qualitative expert interviews, is not fully feasible based on publicly available information. For instance, questions regarding why a company pursues a particular R&D strategy or why a certain M&A transaction was done cannot be answered with this research design.

Although this study focuses on the top 20 pharmaceutical companies by total revenue in 2022, the companies differ significantly in size and, above all, in their R&D performance. Particularly among the smaller Big Pharma firms, such as Novo Nordisk, the number of new approvals between 2011 and 2022 was relatively small, even for descriptive statistics.

Furthermore, our analysis of R&D focused on the invention of the active ingredient. This is the most crucial step in the context of pharmaceutical innovation. However, this indicator does not reflect the full R&D activities of a company. Drug candidates acquired during preclinical or early clinical development are often regarded by the companies involved as internal, given that they must make a substantial financial and intellectual contribution up to market approval. Nevertheless, according to the definition used here, such assets are considered external.

Analyses of R&D productivity need to be discussed in context of 'survivor bias', because the results of R&D focus on successful (approved) new drugs, whereas failed drug candidates are ignored. Given that this study considers the top 20 pharmaceutical companies, which represent successful firms in the industry, and because input-to-output and input-to-outcome analyses are well established in the academic literature,[(p7),(p27),(p28)] survivor bias is not considered to be relevant in the context of this R&D performance analysis.

Another limitation of our analysis concerns the commercialization period. Given that we did not analyze the entire product life cycle of the 237 new drugs examined, there could theoretically be deviations in the R&D outcomes studied.

In addition, the purely qualitative–theoretical presentation of the different R&D models in Figure 2 is not based on a specific framework or on quantitative thresholds. Rather, the figure provides a purely descriptive explanation of the analyzed issue. For example, it cannot be conclusively determined whether the two R&D models 'hybrid' and 'multi-sourced' differ strategically. Both models are based on the use of internal and external innovation and, therefore, could be combined into a single category. Thus, a more detailed analysis of these proposed R&D models could be carried out in future research by developing specific quantitative thresholds and criteria for classification.

Finally, there is a certain path dependency in evaluating R&D performance. Given the long time-span from patent filing to drug approval of on average 14 years,[(p7)] what we are observing today reflects strategic decisions made over a decade ago. Companies might have since adapted or fundamentally restructured their R&D strategies, meaning that today's results might not represent their current strategic position.

TABLE 2

Internal R&D performance of leading pharmaceutical companies (2011–2022)[a]

Company	New drugs (total)	Externally invented drugs	Collaboratively invented drugs	Internally invented drugs	NMEs	NTBs	Other modalities	Standard review process	Priority review process	FIC drugs	No. of target classes	No. of therapeutic areas	New drug sales (US$bn)	New sales ratio
AbbVie	10	6	2	2	2	0	0	1	1	1	2	2	12.1	3%
Amgen	8	5	0	3	1	2	0	2	1	2	2	3	7.1	2%
Astellas	4	2	2	0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	1.0	1%
AstraZeneca	20	14	1	5	3	2	0	1	4	0	4	2	45.3	11%
Bayer	8	2	0	6	6	0	0	1	5	2	4	4	14.6	4%
Biogen	5	3	0	2	1	1	0	2	0	0	2	1	40.4	28%
Boehringer Ingelheim	7	0	0	7	5	2	0	4	3	4	5	4	50.0	16%
Bristol-Myers Squibb	15	9	2	4	3	1	0	2	2	2	3	3	67.2	19%
Daiichi Sankyo	3	1	0	2	1	1	0	1	1	0	1	2	12.0	9%
Eli Lilly	12	6	0	6	3	3	0	5	1	2	3	5	50.8	16%
Gilead Sciences	10	1	6	3	3	0	0	0	3	2	2	1	47.5	15%
GlaxoSmithKline	16	10	1	5	3	2	0	4	1	3	3	2	23.8	4%
Johnson & Johnson	16	9	1	6	2	4	0	1	5	4	3	5	25.5	4%
Merck & Co.	16	12	0	4	4	0	0	2	2	1	3	3	5.9	1%
Novartis	24	11	2	11	10	1	0	5	6	4	4	5	45.1	6%
Novo Nordisk	3	0	0	3	1	2	0	3	0	0	3	1	29.9	12%
Pfizer	17	9	0	8	8	0	0	2	6	2	2	3	63.2	8%
Roche	17	10	1	6	1	5	0	2	4	3	3	4	34.2	4%
Sanofi	12	10	0	2	1	1	0	2	0	1	1	2	18.2	3%
Takeda	14	12	1	1	1	0	0	1	0	0	1	1	6.4	2%
Total	237	132	19	86	59	27	0	41	45	33	–	–	600.2	–
Average	11.9	6.6	1.0	4.3	3.1	1.4	–	2.2	2.4	1.7	2.7	2.8	30.0	8%
Median	12.0	7.5	0.5	4.0	3.0	1.0	–	2.0	2.0	2.0	3.0	3.0	27.7	5%

[a] R&D output and outcome of the top-20 pharmaceutical companies (2011–2022) broken down as number of externally invented new FDA-approved drugs, number of collaboratively invented new FDA-approved drugs, and number of internally invented new FDA-approved drugs. For internally invented new drugs, the following data are reported: sales (US$bn) generated by new drugs, and new sales ratio. In addition, internally invented new drugs are further broken down into number of NMEs, number of NTBs, number of new drugs with other modalities (i.e., not NME or NTB), number of drugs approved under standard review, number of new drugs granted priority review designation, number of FIC drugs, number of drug target classes, and number of therapeutic areas.

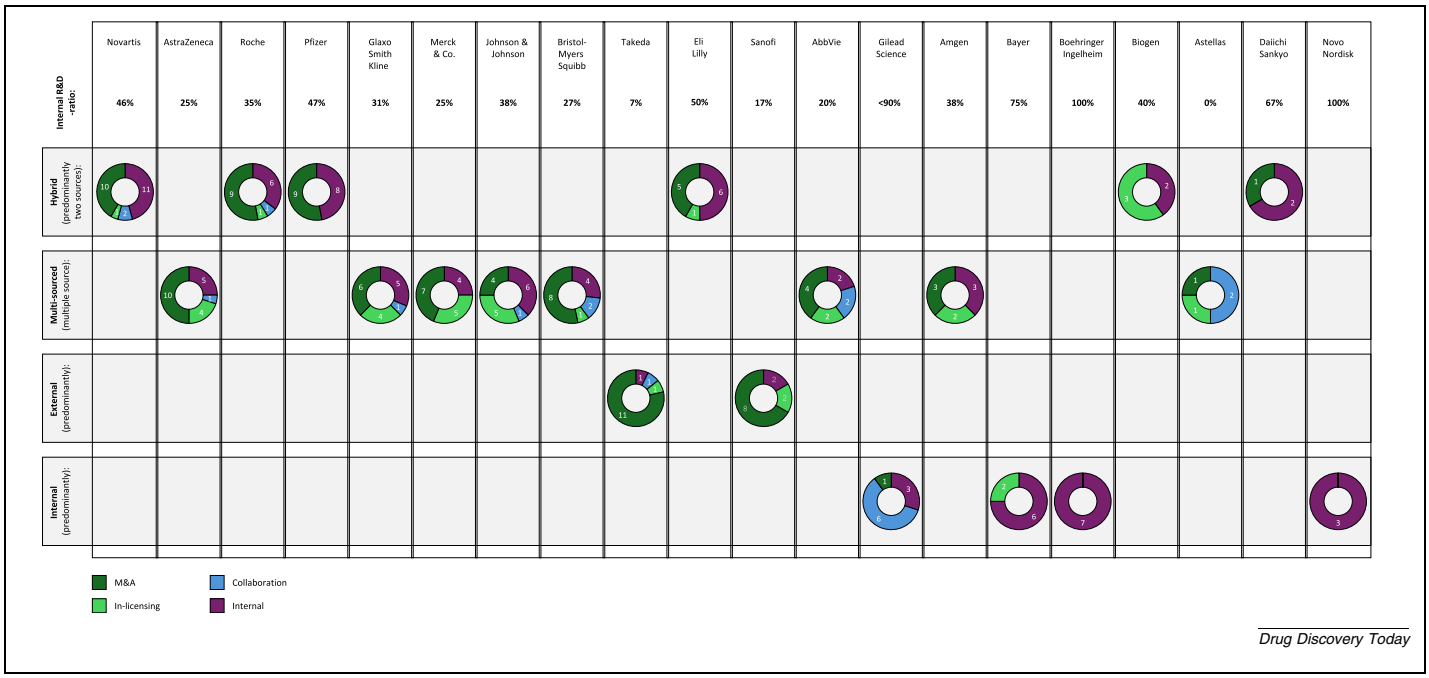

FIGURE 2

Qualitative classification of research and development (R&D) models of leading pharmaceutical companies based on the locus of innovation of FDA-approved new drugs (2011–2022): internal (burgundy), collaborative (blue), and external (green), with the latter further subdivided into in-licensing (light green) and mergers and acquisitions (M&A, dark green). The internal R&D model is defined as one primarily based on internally invented new drugs. The hybrid model relies predominantly on two loci of innovation. In the multi-sourced model, the portfolio of FDA-approved drugs (2011–2022) is distributed across several loci of approximately equal magnitude. By contrast, companies following predominantly externally focused models exhibit a concentration toward external innovation. For the case of Gilead Science, the six collaboratively invented new drugs were considered as being primarily internal. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Concluding remarks and outlook

Commonly used indicators for measuring R&D performance include financial metrics, such as annual R&D expenditures, innovation-related and internal business indicators, such as the number of innovation activities, and alliance or network-based measures.[p27] In this analysis, we analyzed and benchmarked the R&D performance of the 20 leading pharmaceutical companies in terms of their R&D output and outcome, in the context of the origin of innovation.[p7],[p35]

Considering the results of our analyses, several key points can be highlighted: (i) the 20 pharmaceutical companies analyzed invested US$1546.8 billion in R&D between 2011 and 2022. During the same period, newly approved drugs generated revenues of US$1322.8 billion. Even when taking into account that the commercial data do not cover the full product lifecycle of new drugs, it becomes evident that R&D productivity remains a key challenge for the group of the top 20 companies; (ii) the 20 pharma companies received FDA approval for 237 new drugs (2011–2022), averaging 0.99 new drugs per company per year, indicating a pressured R&D performance that is below the commonly cited benchmark of more than two new drugs per company and year required to sustain growth through innovation[p7]; (iii) only 36% of the 237 new drugs were invented internally, indicating why large pharmaceutical companies rely on external innovation; (iv) 69% of internally invented new drugs are small molecules, indicating the technological capabilities of the companies in conventional drug discovery; (v) 56% of new drugs were invented externally, confirming that, for most leading pharmaceutical companies, the business model is built on external innovation[p35]; (vi) in addition, externally acquired assets are partly outside the strategic scope of internal drug discovery, indicating that companies were able to expand their drug target, drug modality, and therapeutic area space through the acquisition of new drugs.

We have four main conclusions. First, in line with the concept of a technological regime,[p36],[p37] wherein companies tend to pursue similar innovation strategies, it can be observed that most of the leading companies work in the same therapeutic areas, address established drug targets, and leverage primarily small molecules as therapeutic modalities. This indicates the path dependencies in R&D in these firms (i.e. R&D models built on established innovation strategies).[p31] It further indicates that the leading companies have historically invested in small molecule-based drug discovery and related technological capabilities, such as high-throughput screening, which are now well established and operate efficiently. This perspective is supported by the fact that the proportion of small molecules among collaboratively invented new drugs was high. To success-

fully collaborate with external partners, it can be assumed that a company needs to have sufficient internal technological capabilities in the relevant research field.

Second, most leading companies make use of external innovation to expand their drug target, therapeutic modality, and therapeutic area spaces. This suggests that external innovation is leveraged not only to address pipeline gaps but also to: (i) expand R&D capabilities; (ii) respond to technological discontinuities; (iii) react to dynamic market trends; or (iv) strengthen life-cycle management activities, while concentrating their internal resources on core activities. For instance, Big Pharma tends to leverage biotech innovators to better manage the science-driven, dynamic, and technology-intensive nature of drug research, and to take opportunities that would not be achievable based solely on their internal R&D organizations.

Third, in the context of the origins of innovation among the 20 companies analyzed, we identified four R&D models. When examining R&D performance within the context of these models, it becomes evident that none of them inherently leads to superior outcomes in terms of the number of new drugs or associated drug sales. This might be due to the relatively short observation period, which does not fully capture complete product life cycles. Accordingly, the four models should be understood as interim outcomes of an ongoing evolutionary process,[p38] in which companies (within the context of the R&D productivity challenge) seek to remain competitive by leveraging their existing internal technological capabilities while complementing them with external innovation. Importantly, these qualitatively described patterns do not represent forward-looking strategies but rather reflect past R&D decisions. In this sense, we assume that companies have already further evolved their R&D organizations toward greater reliance on external innovation. From our perspective, this shift toward increased openness reflects the limited efficiency of internal drug discovery, the need to pursue new growth opportunities, and the dynamic way in which leading companies respond to external technological and market dynamics.

Finally, another important aspect worth considering is the understanding that R&D output (number of new drugs) does not fully capture R&D performance, because R&D outcome (commercial success of new drugs) is equally important. Our analysis showed that the collaboratively invented new drugs yielded higher average annual revenue (US$1.03 bn) compared with fully internally developed new drugs (US$0.90 bn), whereas externally acquired drugs performed significantly lower (US$0.58 bn). Thus, the origin of innovation appears to strongly impact the commercial value of new drugs. Potential mechanisms that might explain these results could be analyzed in more detail in a follow-up research project. Nevertheless, several explanations can already be derived theoretically: (i) pharmaceutical companies pursue R&D not only to develop new drugs, but also to build and enhance their absorptive capacity, that is, the ability to recognize and leverage the value of new external information.[p39] This by-product of R&D positively influences the ability of a firm to innovate,[p40] improves its innovation performance,[p41] leads to better technological capabilities and new innovations, and provides competitive advantage by R&D.[p42] It also represents an essential foundation for conducting successful collaborations.[p42] By contrast, frequent changes in R&D strategy, such as a shift toward greater reliance on external innovation, could lead to reduced absorptive capacity in competitive R&D fields[p43]; (ii) although companies acquiring assets typically conduct extensive due diligence and must have sufficient knowledge in the relevant technological field to ensure successful development, it can nevertheless be assumed that, for internally developed assets, tacit knowledge as well as asset-specific experience are greater. Consequently, the technical and regulatory uncertainties associated with externally acquired assets are likely to be higher than those associated with internally developed drug candidates; (iii) although, in the context of R&D productivity, one can assume a so-called 'survivor bias' for internal candidates,[p8] it can equally be assumed that there is a 'acquisition pressure bias' for external assets, because companies need to fill pipeline gaps in a business environment of limited opportunities and lack of full information. This can lead to valuation uncertainties at the time of acquisition or to technical challenges in post-acquisition integration and, thus, to the lower commercial success of acquired drugs.

In this context, it is worth examining the unique positioning of Gilead Sciences in more detail and discussing to what extent a collaboration-oriented R&D model combined with a focused internal R&D can lead to competitive advantages and improved R&D performance. Theoretically, competitive advantages can result from the sustained development of internal technological capabilities, a deep understanding of biomedical science in the researched field, established patent portfolios, or well-developed R&D ecosystems.

Based on our results and classification, four recommendations can be drawn for pharmaceutical executives in managing R&D: (i) question the purpose of external innovation and reconsider the benefits of focusing on achieving short-term R&D objectives by the acquisition of external assets to fill pipeline gaps; (ii) leverage the potential of drug discovery partnerships, even if they do not support short-term goals; (iii) reconsider the increasingly externally oriented R&D models and invest more in internal R&D and, in particular, build new technological capabilities; and (iv) rebalance the R&D strategy from a focus on R&D efficiency toward a balance between efficiency (output) and effectiveness (outcome).

Given that the industry has been focusing on increasing R&D efficiency for many years,[p10],[p11],[p12],[p13],[p14],[p15] it is worth considering options to improve R&D performance, specifically in the context of competitive advantage and future growth. According to Porter, competitive advantage is not about being better than competitors but rather about to create superior performance by uniqueness.[p44] In our view, uniqueness in the biomedical field can be achieved by[p45],[p46]: (i) developing new drugs with a perceived high medical value, such as by innovative drugs granted priority review or breakthrough

therapy designations; (ii) providing innovation that is hard to imitate, such as by complex NTBs or cell therapies; and (iii) protect what makes the company different through market barriers, such as by proprietary technologies or unique internal technological capabilities.

If a company is able to derive a real competitive advantage, it means, that it can operate R&D at lower costs compared with its competitors, or achieve a premium price for new drugs, or both, thereby improving R&D productivity (efficiency and effectiveness).[(p44)]

Looking forward, the pharmaceutical industry is undergoing a fundamental shift, driven by both the persistent R&D productivity crisis and recent geopolitical developments.[(p47),(p48)] Leading firms have moved from a Fully Integrated Pharma Company (FIPCO) to open business models of Fully Integrated Pharma Networks (FIPNets) and Biotech-leveraged Pharma Companies (BIPCOs).[(p35),(p49),(p50),(p51)] Although low R&D productivity still calls for greater efficiency and, thus, more reliance on external innovation, the commercial success of internal and collaborative approaches challenges this logic. In addition, new policies, such as the Most Favored Nation (MFN) pricing, might shift strategic focus toward commercial goals. Therefore, it remains to be seen which R&D model (internal, external, hybrid, or multi-sourced) will prevail in the years ahead.

Declaration of interests

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CRediT authorship contribution statement

Alexander Schuhmacher: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Oliver Gassmann:** Writing – review & editing, Writing – original draft, Conceptualization. **Sara Knapp:** Writing – original draft, Formal analysis, Data curation. **Dominik Hartl:** Writing – review & editing, Writing – original draft, Conceptualization. **Markus Hinder:** Writing – review & editing, Writing – original draft, Conceptualization.

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