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Analysis of pharma R&D productivity – a new perspective needed

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R&D productivity continues to be the industry's grand challenge. We analyzed the R&D input, output, and outcome of 16 leading research-based pharmaceutical companies over 20 years (2001–2020). Our analysis shows that pharma companies increased their R&D spending at a compound annual growth rate of 6% (2001–2020) to an average R&D expenditure per company of $6.7 billion (2020). The companies in our investigation launched 251 new drugs representing 46% of all CDER–related FDA approvals in the past 20 years. The average R&D efficiency of big pharma was $6.16 billion total R&D expenditures per new drug. Almost half of the leading companies needed to compensate for their negative R&D productivity through mergers and acquisitions.

Keywords: big pharma; drug discovery; R&D; R&D efficiency; R&D effectiveness; R&D productivity

Introduction

The business model of leading pharmaceutical companies, the logic of value creation, is built on creating and delivering a steady flow of novel, patented, and medically attractive drugs and capturing commercial value out of R&D.[1–4] Over the past 20 years, it became obvious that the industry's R&D productivity, defined as the ratio of commercial value of new drugs to the related investments in drug discovery and development, remains a key challenge.[5–7] As the return-on-investment rate in R&D declined continuously, it led to the conclusion that the industry's business model is under pressure.[8,9].

An estimated average pre-approval R&D cost of $2.6 billion per new drug (in 2013 $) or more ($2.9 billion if including Phase IV trials), high attrition rates in R&D, long cycle times, and failures in efficiently leveraging drug discovery technologies are factors indicating that R&D productivity is a Sisyphean undertaking for the industry.[5,10–15] In fact, the pharmaceutical industry faced an exceptional slowdown and productivity downturn between 2005 and 2011.[16] From 2000 to 2010, the market value of the top 20 pharmaceutical companies decreased by 30%.[17] Indicated by the expected average peak sales per new drug, the R&D outcome (2000-2019) decreased particularly for new oncology products because of smaller market segments per approval.[18] It has been described that the decrease in R&D productivity is driven primarily by the increasing R&D spend of the industry,[19] with a bigger part of costs in pharmaceutical R&D being caused by failed R&D projects.[5] One aspect of the reduced R&D productivity is R&D efficiency, that is, the relationship of R&D

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costs (input) to the number of new drugs created by R&D (output).[5]

Recent findings, however, indicate that the industry's R&D efficiency is recovering.[20,21] This trend may be caused by a slight turnaround in R&D timing and attrition.[21] Advanced integration of human genetics and multi-omics technologies, a trend toward mechanistic studies in smaller patient populations, and an increasing 'truth-seeking' (rather than 'progression-seeking') behavior might be factors in breaking the 'Eroom's law'.[21–24] A better scientific understanding of disease biology/disease mechanisms, improved target selection, better target validation, improved pharmacokinetic/pharmacodynamic modeling, biomarkers, and patient stratification are parameters of an increasing R&D efficiency.[25] The high number of drug approvals by the Center of Drug Evaluation and Research (CDER) of the FDA in 2020 and 2021 provided further evidence that R&D efficiency is not declining further.[26,27] However, the industry witnessed only 37 new drugs approved by the FDA in 2022, the lowest number since 2016.[28]

Inspired by these controversies, we aimed to comprehensively assess the R&D productivity of 16 leading pharmaceutical companies by sales (2020) and to obtain systematic insights into the ability of pharmaceutical companies to commercially profit from R&D. By reviewing corporate data as well as assessing and dissecting the state-of-the-art, our study illustrates that R&D productivity remains a core challenge of big pharma companies (for definitions, data source, and analyses, see Supplementary information S1 online).

R&D input of big pharma

The 16 leading pharmaceutical companies included in our study represent the largest and globally active research-based pharmaceutical firms that cover the entire value chain from drug discovery to development and commercialization of new drugs and are thus often termed 'big pharma'.[29,30] In 2020, their cumulative sales of $510.6 billion represented 61.7 % of the 2020 total prescription market of $827 billion (Table 1).[31] Big pharma witnessed a considerable market growth in the past two decades. While the average annual total revenue per company was $19.1 billion (2001–2005), the leading companies grew at a compound annual growth rate (CAGR) of 6% to an average annual commercial result of $29.7 billion (2016–2020) (Table 1).

In contrast to other industries, R&D is a major competitive factor in the pharmaceutical sector, and there is an association between R&D growth and sales growth for pharmaceutical companies.[32] The 16 leading pharma companies in our investigation invested a total of $1,539.9 billion in R&D between 2001 and 2020 (Table 1), with a significant increase in R&D spending over time from $249.7 billion (2001–2005) to $476.7 billion (2016–2020). Apart from GlaxoSmithKline (GSK; CAGR − 1%), all leading companies increased their R&D spending over the past 20 years (CAGR + 6%; Table 1), resulting in an average R&D expenditure per company of $6.7 billion (2020). This translates into a big pharma R&D intensity (2020), that is, the proportion of R&D spending to total sales of a company, of an average of 20%. In this context, it is worth mentioning that GSK's recent R&D intensity (2016–2020) of 13% is clearly below the typical range of other leading companies with a comparable R&D portfolio. Because there is economy of scale in R&D,[33] an R&D intensity below benchmark could negatively impact the output of R&D in the long run.

R&D output and outcome of big pharma

The typical aim of a productive R&D organization is to translate its R&D input into the highest possible R&D output. The companies in our investigation launched 251 new molecular entities (NMEs) and new therapeutic biologics (NTBs) between 2001 and 2020, representing 46% of all CDER-related FDA approvals in that time frame (Figure 1). The annual R&D output for all 16 leading companies ranged from a minimum of 7 (2010) to a maximum of 22 new FDA-approved drugs (2015), with a 20-year annual average of 12.6 NMEs/NTBs approved for the 16 companies in our investigation. Although we saw a considerable increase from an average annual output of 9.1 new drugs (2001–2010) to 15.7 (2011–2020), there is a trend of a declining relative proportion of FDA-approved drugs by big pharma from 76% (2001) to 25% (2020) (Figure 1).

On average, a big pharma company received 0.78 FDA-approvals per year (2001–2020), with Novartis having the highest 20-year average output of 1.5 new drugs per year (Supplementary information S3 online). Specifically, Novartis launched 1.3 new drugs per year (2001–2015) and increased its annual output to two NMEs/NTBs in the last 5 years (2016–2020).

In our analyses, we differentiated between 'proprietary' and 'in-licensed' new drugs, as well as new drugs that were acquired by merger and acquisition (M&A) pre- and post-approval. Proprietary drug discovery contributed to nearly half (138) of all NMEs/NTBs (2001–2020). Licensing (56) and M&A (pre-approval, 57) complemented the R&D output of the investigated companies (Supplementary information S3 online). Although proprietary R&D outweighed licensing and M&A between 2001 and 2007, a notable increase in licensing deals and pre-approval M&A activities was observed between 2009 and 2015 (Figure 1).

Our analysis also included 57 new drugs for which the companies in our investigation were not listed as the original applicant at the FDA, but which resulted from post-approval M&A activities. Merck & Co., Pfizer, and Bristol-Myers Squibb (BMS) acquired a significant number of new drugs that did not originate from their own R&D. Takeda was the only company in our analysis that relied on post-approval M&A as their main source for new drugs (Supplementary information S3 online).

Although new FDA approvals are a direct measure of the output of R&D, sales resulting from new drug launches are a quote of the outcome of R&D and an important corporate growth indicator. The 251 new drug launches generated $1,796.4 billion revenue (2001–2020), representing 25% of total sales of the 16 investigated companies (Supplementary information S3 online). Nominally, Amgen, Novartis, and BMS benefited most from new drug sales, whereas GSK, Takeda, and Bayer profited least from new innovation (Supplementary information S3 online). Relatively, Amgen (59%) and Gilead (52%) exceeded other peers, whereas new drug sales did not impact total sales of Sanofi (8%) and GSK (6%) much. The commercial success of new drug launches of big pharma companies was driven primarily by proprietary new drugs and, to a smaller extent, by licensing and M&A (Supplementary information S4 online).

TABLE 1

Revenue and R&D figures of leading pharmaceutical companies (2001–2020).

	Total revenue ($ billion)							R&D expenditure ($ billion)							R&D intensity (avg.)				
	Total	Avg. annual	2001–2005	2006–2010	2011–2015	2016–2020	CAGR	Total	Avg. annual	2001–2005	2006–2010	2011–2015	2016–2020	CAGR (%)	Avg. annual	2001–2005	2006–2010	2011–2015	2016–2020
Pfizer	1075.2	53.8	249.1	288.0	286.0	252.2	1%	166.5	8.3	39.2	45.5	41.9	39.9	1%	16%	16%	16%	15%	16%
GSK	795.9	39.8	213.5	237.6	185.0	159.8	−1%	118.2	5.9	33.1	38.9	25.1	21.2	−1%	15%	15%	16%	13%	13%
Merck & Co.	720.9	36.0	149.7	159.0	213.0	199.2	2%	158.1	7.9	22.0	37.9	42.8	55.6	7%	22%	15%	23%	20%	28%
Sanofi	678.4	33.9	104.6	206.4	189.4	178.0	8%	111.7	5.6	14.0	34.9	33.0	29.8	8%	17%	15%	17%	17%	17%
Roche	649.8	32.5	79.5	159.7	188.4	222.2	8%	146.3	7.3	15.3	33.8	43.2	54.0	10%	22%	19%	21%	23%	24%
J&J	635.9	31.8	130.7	142.8	158.0	204.4	4%	128.2	6.4	22.3	29.6	32.7	43.5	5%	20%	17%	21%	21%	21%
AstraZeneca	589.3	29.5	133.9	186.2	153.7	115.6	1%	113.4	5.7	21.9	30.5	30.4	30.6	2%	20%	16%	17%	20%	27%
Novartis	549.4	27.5	84.5	130.3	158.5	176.0	6%	112.9	5.6	15.5	26.6	34.2	36.6	6%	20%	18%	20%	22%	21%
BMS	440.9	22.0	104.5	103.5	98.3	134.7	3%	95.7	4.8	15.7	19.5	24.4	36.1	6%	22%	15%	19%	25%	27%
Eli Lilly	415.1	20.8	81.7	113.8	110.1	109.5	2%	89.8	4.5	16.0	22.5	25.4	26.2	4%	22%	20%	20%	23%	24%
Amgen	356.3	17.8	51.8	87.2	100.9	116.4	8%	69.9	3.5	10.8	17.8	21.2	20.1	6%	20%	22%	20%	21%	17%
Bayer	296.3	14.8	32.4	80.4	83.2	100.3	6%	48.2	2.4	6.4	12.5	12.9	16.6	4%	17%	20%	16%	15%	17%
Takeda	293.6	14.7	36.6	62.5	82.6	111.9	9%	56.5	2.8	5.5	14.7	18.2	18.1	9%	19%	15%	23%	22%	17%
Boehringer	272.4	13.6	41.8	75.5	78.0	77.1	5%	48.9	2.4	6.6	13.0	15.1	14.2	6%	18%	16%	17%	19%	18%
Gilead	258.7	12.9	6.0	30.4	93.9	128.3	25%	40.6	2.0	1.4	4.5	12.2	22.6	16%	20%	37%	15%	15%	18%
NovoNordisk	247.0	12.3	26.8	50.6	77.9	91.6	8%	34.9	1.7	4.1	8.3	11.0	11.5	7%	15%	15%	16%	14%	13%
Total	8275.1		1527.1	2113.9	2256.9	2377.2		1539.9		249.7	390.5	423.7	476.6						
Average	517.2		95.4	132.1	141.1	148.6	6%	96.2		15.6	24.4	26.5	29.8	6%	19%	18%	19%	19%	20%
Average annual	25.9		19.1	26.4	28.2	29.7		4.8		3.1	4.9	5.3	6.0						

To illustrate the revenue figures simply, we consolidated the data to the quinquennial periods of 2001–2005, 2006–2010, 2011–2015, and 2016–2020. For annual details, see Supplementary Information S2 online.

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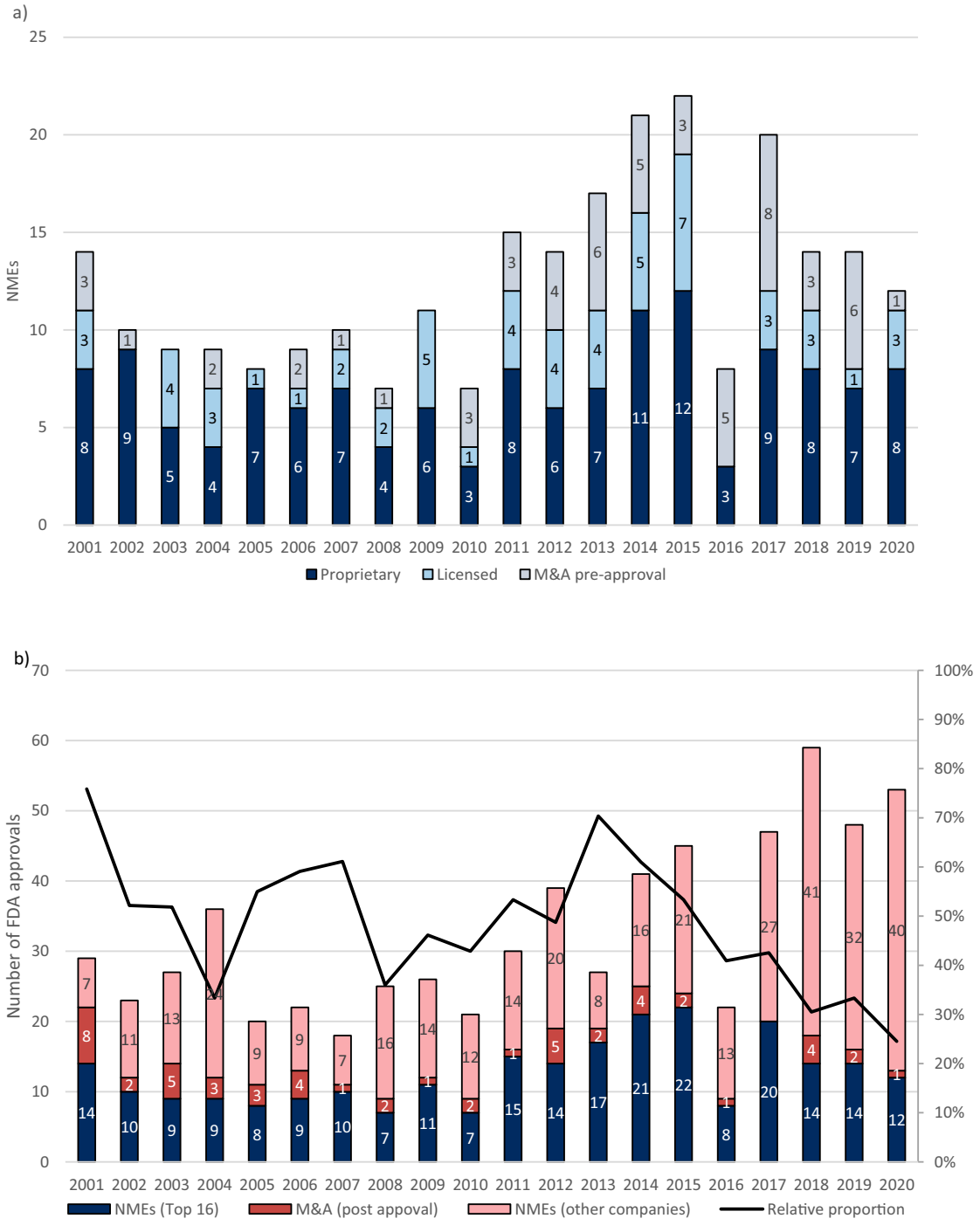

FIGURE 1

R&D output (2001–2020) of leading pharmaceutical companies. (a) Cumulative FDA-approved NMEs/NTBs per year and origin (proprietary, licensed, or acquired before approval). (b) Absolute and relative proportion of the sample of 16 leading pharmaceutical companies to the overall FDA new drug approvals (2001–2020). Source of CDER-related FDA approvals: https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products. Abbreviations: CDER, Center of Drug Evaluation and Research; FDA, Food and Drug Administration; M&A, merger and acquisition; NMEs, new molecular entities; NTBs, new therapeutic biologics.

R&D efficiency and R&D productivity of big pharma

R&D efficiency is a key indicator of how productively an R&D organization uses its allocated resources and is an indicator of how much money it takes to discover and develop a new drug. Typically, for a specific project, the drug cost estimates result from the capitalization of direct costs of a new drug over the long-lasting period of drug discovery and development of often more than ten years.[5,10] Because

cost estimations for NMEs/NTBs are complex and subject to debate, a simple method to analyze the R&D efficiency of a pharmaceutical company is to divide its annual R&D spending by the number of its new drug launches.[34] Because there is a time gap of R&D spending and R&D output of a reported 5 years,[10] we applied this method in a 20-year time frame and could show that the peer group's R&D efficiency (2001–2020) is $ 6.16 billion – more than double the estimated pre-approval R&D costs per NME.[10] Only Gilead ($3.13 billion) and Novartis ($3.76 billion) had 20-year R&D efficiencies comparable with the commonly cited figure of $2.6 billion ($2.9 billion if including Phase IV trials) (Supplementary information S5 online).

In line with a broader definition of innovation,[35] commercialization of a drug is what leverages the invention and turns a drug candidate into an innovation. We therefore analyzed the R&D effectiveness, namely the commercial outcome per new drug. On average, the R&D effectiveness of big pharma was $7.57 billion (average commercialization time of 8 years) per new drug, with Amgen ($14.96 billion/9.6 years), Novo Nordisk ($12.33 billion/7.5 years), and BMS ($11.78 billion/6.9 years) having generated significantly higher outcome with their R&D output than GSK ($2.76 billion/4.7 years), Bayer ($2.77 billion/8.5 years), Sanofi ($3.37 billion/7.3 years), or Takeda ($3.91 billion/6.3 years) (Supplementary information S5 online).

We further calculated the R&D productivity of big pharma by setting the average revenue resulting from new drug launches (2001–2020) in proportion to the overall coprorate R&D costs per NME (2001–2020) (Figure 2). Nine of the 16 leading pharma companies, namely Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, Gilead, Johnson & Johnson, Novartis, and Novo Nordisk had a positive R&D productivity, indicating that the companies were successful not only in discovering, developing, and launching new drugs but also in commercializing them. Bayer, GSK, Merck & Co., Pfizer, Roche, Sanofi, and Takeda had a negative 20-year R&D productivity (Figure 2), of which six companies were able to compensate for their negative input/outcome ratio

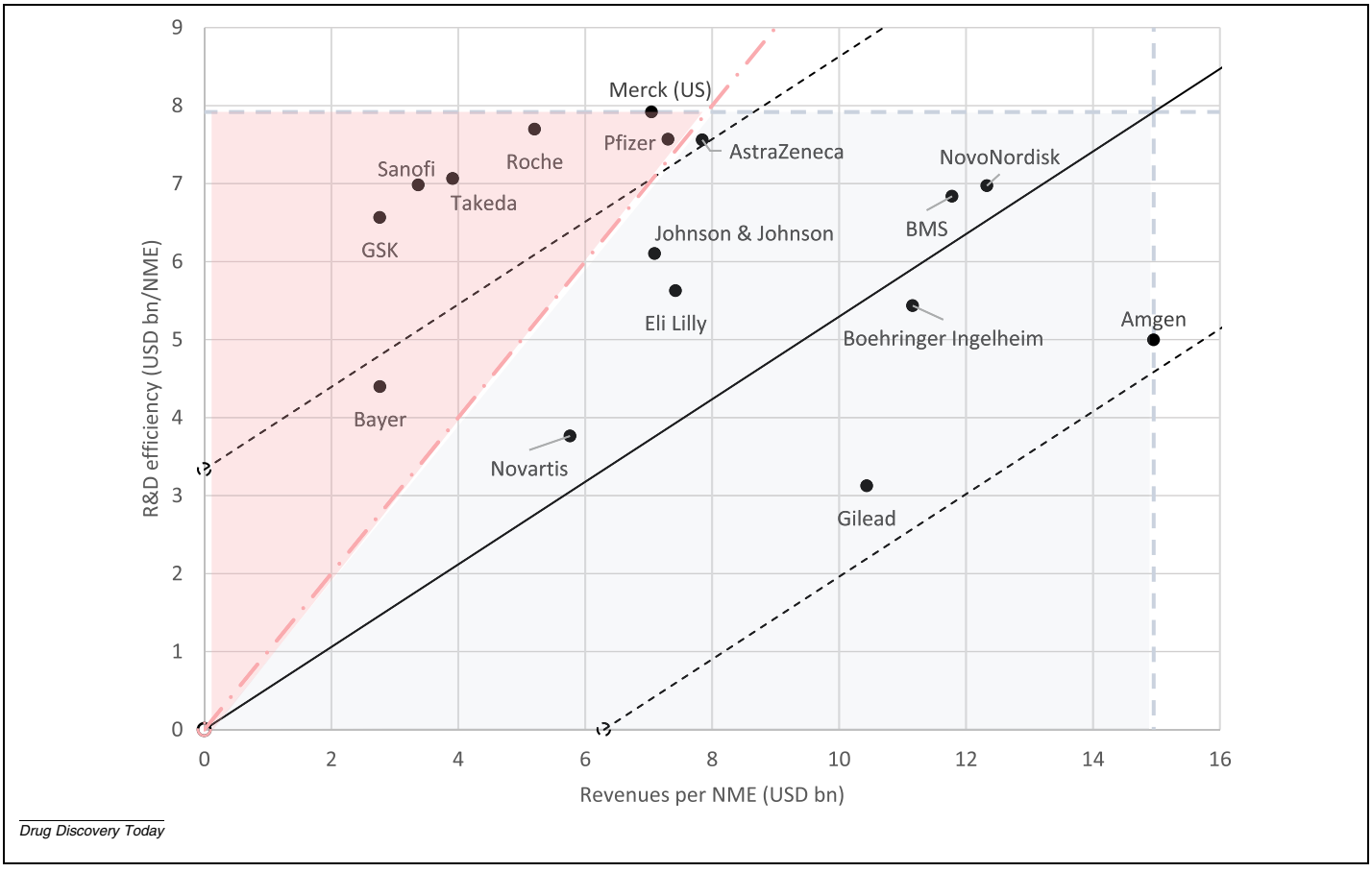

FIGURE 2

R&D productivity of leading pharmaceutical companies (2001–2020). The R&D productivity of our sample group of leading pharmaceutical companies classified by plotting the R&D efficiency (2001–2020) against the revenues by NMEs/NTBs launched 2001–2020. As a reference and orientation line, a straight black line is drawn from zero (no input and no outcome) to the coordination point in the chart that represents the maximum R&D efficiency/maximum revenue per NME in the given sample. The standard deviation of the companies' distance to the standard line determines the border (dashed black lines) of three groups, which represents companies that have a lower R&D productivity (e.g., Sanofi), standard R&D productivity (e.g., Novartis), or higher R&D productivity than the standard of the sample. The dotted pink line illustrates if a company was able to break even on their R&D spending. Abbreviations: NMEs, new molecular entities; NTBs, new therapeutic biologics.

through acquisitions of previously approved drugs (or full mergers with other companies) (Supplementary information S5 online). Takeda was the only leading company in our investigation that failed to manage a positive R&D productivity (2001–2020).

Sample representativeness and limitations

This study analyzed and described the R&D input, output, and outcome (2001–2020) of 16 of the leading pharmaceutical companies representing almost two-thirds of the 2020 total prescription market. Our findings and conclusions may not be valid for pharmaceutical companies of other sizes and different business models. Smaller research-driven companies operating in geographic or therapeutic niches may have special levers and challenges other than the ones discussed herein.

It is important to mentioned that there are debates about the methods used to calculate costs of drug discovery and development and to measure R&D efficiency. For example, because there is a time delay between R&D spending (input) and approval of a new drug (R&D output), DiMasi et al. proposed a 5-year time lag to be applied in cost estimations.[10] We decided to use the methodology established by Munos and to overcome the limitation of time lag by analyzing R&D productivity over a period of 20 years, thus covering more than one R&D life cycle.[34]

Although there is inconsistency between companies, R&D spending used in our analysis may include costs for Phase IV trials and thus, at least to some extent, describe the difference of R&D efficiency in our study from the estimated average pre-approval costs per new drug. In addition, spending for biomedical and digital technology development, expenses for technology implementation, overhead costs, costs for patent protection, or expenditures for alliance management may be further factors explaining the variance.

Our analysis period (2001–2020) encompassed parts of the COVID-19 pandemic (2019/2020), which had an overall major impact on the pharmaceutical sector at different levels (shift of R&D activities toward COVID-19 antiviral and vaccination approaches, disrupted clinical trials, challenging supply chain management, and others). Although our results do not allow conclusions on specific COVID-19-related R&D metrics, the concomitant temporal effects on the pharmaceutical ecosystem within that time frame may limit the generalizability of some of our broader R&D conclusions.

Concluding remarks and outlook

On the basis of our numerical analyses, we conclude the following key finding: R&D productivity remains a grand challenge for big pharma. The 16 leading companies in our investigation invested more than $1.5 trillion in drug discovery and development and launched 251 new drugs between 2001 and 2020. On average, a big pharma company spent $4.4 billion annually in R&D and launched 0.78 new drugs (2001–2020). The peer group's R&D efficiency (2001–2020) is $6.16 billion (total R&D spending per new drug launch). Almost half of the leading companies failed to have an R&D outcome (2001–2020) (i.e., commercial value of new drug launches) that compensated for the enormous R&D costs. Seven of 16 companies in our investigation needed to compensate for their negative R&D input/outcome ratio through M&As. In this context, we recently demonstrated that 57% of all new drug launches (2011–2020) by big pharma were R&D unprofitable.[4] At first glance, these figures pose the question whether big pharma's R&D results adequately represent its aspirations to sustain corporate growth by R&D.

Thus, in view of the challenging R&D productivity, big pharma companies need to meet the challenge of building a sustainable business model in R&D that can cope with its growth aspiration, the strategic risks of R&D, and the technical uncertainties of drug discovery and development in the long term.

Big pharma's business model is programmed on launching blockbuster drugs.[4] An aspect worth acknowledging is that once a blockbuster model is established in R&D, it sets the strategic and commercial benchmarks that are hard to ignore or to bypass. As the path dependence theory highlights,[36] the historical track of a company has preprogrammed consequences for future corporate decisions. A fundamental change in a company's blockbuster model is hard to manage[37] and inordinately more difficult to achieve in an industry that is dominated by very stringent pharmaceutical regulations that set standards for high quality, safe, and effective new drugs.

Following the idea of the innovative capability – innovation – firm performance path,[38,39] a new perspective and more fundamental considerations are needed when it comes to the question of how to improve R&D productivity and build a sustainable business model in R&D. Albeit we understand that some of the proposed changes may already be happening in some firms, we suggest that open innovation, digital technologies, dynamic capabilities, absorptive capacities, and value-based project portfolio management are key enablers of a sustainable business model in R&D.

In one of our previous publications, we illustrated that pharmaceutical companies profit from running large and diversified R&D organizations.[33] Greater R&D efficiency can result from economies of scale (R&D size), because companies can take advantage of a lower cost of capital, higher portfolio diversity, or tacit aggregate knowledge. Because only the biggest pharma companies have the funds to run large and complex R&D organizations in the long term or to invest money in high-volume M&A transactions, second- and third-tier companies need to build external R&D ecosystems (i.e., R&D models that integrate large numbers of external contributors) to gain a competitive edge from R&D efficiency.[33,40] Thus, an aspect worth considering in the context of a sustainable business model (at least for some of the leading companies) is open innovation.[41] In this context, pharmaceutical companies have been predicted to pivot strategically from being internal R&D engines toward knowledge integrators.[42] That concept is being advanced by adopting the role of an R&D financier, regulatory liaison, and commercial expert for publicly funded medical research and by building networks with specific collaboration partners.[40,43] However, the industry still has unused potential as only some players started to build R&D ecosystems to fully benefit from external knowledge and propensity of innovation.[40]

Another key feature to consider when improving R&D productivity is digital technology. Real-world data, predictive methods, and artificial intelligence (AI)-

enabled clinical trial designs are described as key enablers of a better R&D.[44–46] During the last few years, generative AI has proved to be a promising technology in lead discovery,[47–49] and recent progress with OpenAI indicates additional potential that has not been tapped yet.[50] As highlighted by Insilico Medicine, there are use cases of AI-designed drug candidates that were discovered from the start of drug discovery to Phase I in 30 months.[51]

Next, as pharmaceutical companies need to dynamically respond to their changing technological environment through their internal capabilities, we consider dynamic capability as a mission-critical element to build a sustainable business model in R&D.[52] It is defined as 'the ability to integrate, build, and reconfigure internal and external competences to address rapidly changing environments'.[53] While leading companies manage their complexities along the entire R&D value chain differently to be competitive, it becomes more important for them to invest in their dynamic capabilities.[53] Dynamic capabilities even might become more important when it comes to more AI partnerships or digital health alliances – AI and tech are expected to strongly influence pharma and healthcare innovation in the next two decades.[54–56]

Closely related to the theory of dynamic capabilities, pharmaceutical companies also need to improve their absorptive capacities; that is, 'the ability of a firm to recognize the value of new, external information, assimilate it, and apply it to commercial ends'.[57] Such an increased learning from outside of the company is exemplified by the collaboration of Pfizer and BioNTech,[58] where both companies expanded their limits of absorption of technological and scientific information. Only companies that recognize the value of new external information, assimilate it, and apply it commercially and that integrate, build, and reconfigure internal and external competencies to address rapidly changing environments will succeed in the long term and master the challenge of R&D productivity.

Finally, managing R&D project portfolios actively and investing in the right scientific opportunities from both internal and external sources is described to positively impact R&D.[7,59] In our view, matter is not only created by the number of new drugs, but by the commercial value of new drug launches. Although there is certainly inaccuracy in forecasting blockbuster launches,[60] we suggest that pharma companies should adjust their R&D portfolios, deprioritize 'me-too' drug candidates, and focus more on those drugs that are innovative in a broader line of definition.[35] All things considered, it is the medical and commercial outcomes of new drug launches that determine the effectiveness of an R&D organization. As exemplified by AbbVie and its blockbuster Humira, the therapeutic advantage and breadth of indications can result in a commercially successful best-in-class scenario that overcompensates for less effective R&D results.[4,61]

Data availability

All data have been made accessible as supplementary information S2–S5.

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This article is partially based on an unpublished master's thesis *R&D models of leading pharmaceutical companies – a 20-year analysis* by A. von Stegmann und Stein, University of St. Gallen.

Declarations of interest

A.S., A.v.S., and O.G. declare no competing interests. M.H. is an employee of Novartis and a former employee of Roche and Sanofi. D.H. is a former employee of Roche and Novartis. This study did not get any external funding and was undertaken independently.

Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.drudis.2023.103726.

References

1. Roberts EB. What we've learned: managing invention and innovation. *Res Technol Manag*. 1988;31:11–29 http://www.jstor.org/stable/24124755.
2. Teece DJ. Business models, business strategy and innovation. *Long Range Plann*. 2010;43:172–194.
3. Lakdawalla DN. Economics of the pharmaceutical industry. *J Econ Lit*. 2018;56:397–449. https://doi.org/10.1257/jel.20161327.
4. Schuhmacher A, Hinder M, Boger N, Hartl D, Gassmann O. The significance of blockbusters in the pharmaceutical industry. *Nat Rev Drug Discov*. 2023;22:177–178. https://doi.org/10.1038/d41573-022-00213-z.
5. Paul SM et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat Rev Drug Discov*. 2010;9:203–214. https://doi.org/10.1038/nrd3078.
6. Scannell JW, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat Rev Drug Discov*. 2012;11:191–200. https://doi.org/10.1038/nrd3681.
7. Ringel MS. What is the right amount to spend on biopharma R&D? *Nat Rev Drug Discov*. 2017;16:597–598. https://doi.org/10.1038/nrd.2017.114.
8. Stott K. Pharma's broken business model: an industry on the brink of terminal decline. EndpointNews; 2017. https://endpts.com/pharmas-broken-business-model-an-industry-on-the-brink-of-terminal-decline/. Accessed December 28, 2022.
9. de Felice, D. How Pharma Can Fix Its Reputation and Its Business at the Same Time. Havard Business Review; 2017. https://hbr.org/2017/02/how-pharma-can-fix-its-reputation-and-its-business-at-the-same-time. Accessed May 3, 2023.
10. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. *J Health Econ*. 2016;47:20–33. https://doi.org/10.1016/j.jhealeco.2016.01.012.
11. Schlander M, Hernandez-Villafuerte K, Cheng CY, Mestre-Ferrandiz J, Baumann M. How much does it cost to research and develop a new drug? A systematic review and assessment. *Pharmacoeconomics*. 2021;39:1243–1269. https://doi.org/10.1007/s40273-021-01065-y.
12. Dowden H, Munro J. Trends in clinical success rates and therapeutic focus. *Nat Rev Drug Discov*. 2019;18:495–496. https://doi.org/10.1038/d41573-019-00074-z.
13. Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. *Biostatistics*. 2019;20:273–286. https://doi.org/10.1093/biostatistics/kxx069. Erratum in: *Biostatistics*. 2019;20(2):366.
14. Thomas D, et al. Clinical Development Success Rates and Contributing Factors 2011-2020. BIO. QLS Advisors. Informa; 2021. https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf. Accessed January 2, 2022.
15. Macarron R et al. Impact of high-throughput screening in biomedical research. *Nat Rev Drug Discov*. 2011;10:188–195. https://doi.org/10.1038/nrd3368.
16. Smietana K, Ekstrom L, Jeffery B, Møller M. Improving R&D productivity. *Nat Rev Drug Discov*. 2015;14:455–456. https://doi.org/10.1038/nrd4650.
17. Tollman P, Morieux Y, Murphy JK, Schulze U. Identifying R&D outliers. *Nat Rev Drug Discov*. 2011;10:653–654. https://doi.org/10.1038/nrd3555.
18. Baedeker M, Ringel MS, Schulze U. Value of 2019 FDA approvals: back to the recent average. *Nat Rev Drug Discov*. 2019;19:85. https://doi.org/10.1038/d41573-020-00002-6.
19. Schulze U, Baedeker M, Chen YT, Greber D. R&D productivity: on the comeback trail. *Nat Rev Drug Discov*. 2014;13:331–332. https://doi.org/10.1038/nrd4320.
20. Laermann-Nguyen U, Backfisch M. Innovation crisis in the pharmaceutical industry? A survey. *SN Bus Econ*. 2021;1:164. https://doi.org/10.1007/s43546-021-00163-5.
21. Ringel MS, Scannell JW, Baedeker M, Schulze U. Breaking Eroom's Law. *Nat Rev Drug Discov*. 2020;19:833–834. https://doi.org/10.1038/d41573-020-00059-3.
22. Ringel M, Tollman P, Hersch G, Schulze U. Does size matter in R&D productivity? If not, what does? *Nat Rev Drug Discov*. 2013;12:901–902. https://doi.org/10.1038/nrd4164.

23. Scannell JW, Bosley J. When quality beats quantity: decision theory, drug discovery, and the reproducibility crisis. *PLoS One*. 2016;11. https://doi.org/10.1371/journal.pone.0147215 e0147215.
24. Tollman P, Panier V, Dosik D, Biondi P, Cuss F. Organizational effectiveness: a key to R&D productivity. *Nat Rev Drug Discov*. 2016;15:441–442. https://doi.org/10.1038/nrd.2016.91.
25. Morgan P et al. Impact of a five-dimensional framework on R&D productivity at AstraZeneca. *Nat Rev Drug Discov*. 2018;17:167–181. https://doi.org/10.1038/nrd.2017.244.
26. Baedeker M, Ringel M, Schulze U. 2020 FDA approvals: momentum kept despite COVID-19, but value falls. *Nat Rev Drug Discov*. 2021;20:92. https://doi.org/10.1038/d41573-021-00016-8.
27. Baedeker M, Ringel MS, Schulze U. 2021 FDA approvals: value driven by COVID-19 vaccines. *Nat Rev Drug Discov*. 2022;21:90. https://doi.org/10.1038/d41573-022-00015-3.
28. Mullard A. 2022 FDA approvals. *Nat Rev Drug Discov*. 2023;22:83–88. https://doi.org/10.1038/d41573-023-00001-3.
29. Capo F, Brunetta F, Boccardelli P. Innovative business models in the pharmaceutical industry: a case on exploiting value networks to stay competitive. *Int J Eng Bus Manag*. 2014;6. https://doi.org/10.5772/59155.
30. Gautam A, Pan X. The changing model of big pharma: impact of key trends. *Drug Discov Today*. 2016;21:379–384. https://doi.org/10.1016/j.drudis.2015.10.002.
31. R. Waters, L. Urquhart, Evaluate Pharma – World Preview 2020, Outlook 2025. Evaluate Pharma, 2021. https://www.evaluate.com/thought-leadership/pharma/evaluatepharma-world-preview-2020-outlook-2026. Accessed January 5, 2023.
32. Tubbs M. The relationship between R&D and company performance. *Res Technol Manag*. 2007;50:23–30 http://www.jstor.org/stable/24135251.
33. Schuhmacher A, Wilisch L, Kuss M, Kandelbauer A, Hinder M, Gassmann O. R&D efficiency of leading pharmaceutical companies – A 20-year analysis. *Drug Discov Today*. 2021;26:1784–1789. https://doi.org/10.1016/j.drudis.2021.05.005.
34. Munos B. Lessons from 60 years of pharmaceutical innovation. *Nat Rev Drug Discov*. 2009;8:959–968. https://doi.org/10.1038/nrd2961.
35. Singh S, Aggarwal Y. In search of a consensus definition of innovation: a qualitative synthesis of 208 definitions using grounded theory approach. *Innovation*. 2022;35:177–195. https://doi.org/10.1080/13511610.2021.1925526.
36. David PA. Clio and the economics of QWERTY. *Am Econo Rev*. 1985;75:332–337 http://www.jstor.org/stable/1805621.
37. Garud R, Kumaraswamy A, Karnøe P. Path dependence or path creation? *J Manag Stud*. 2010;47:760–774. https://doi.org/10.1111/j.1467-6486.2009.00914.x.
38. Roberts PW. Product innovation, product–market competition and persistent profitability in the US pharmaceutical industry. *Strateg Manag J*. 1999;20:655–670 http://www.jstor.org/stable/3094134.
39. Rajapathirana RPJ, Hui Y. Relationship between innovation capability, innovation type, and firm performance. *J Innov Knowl*. 2018;3:44–55. https://doi.org/10.1016/j.jik.2017.06.002.
40. Schuhmacher A, Gassmann O, Bieniok D, Hinder M, Hartl D. Open innovation: a paradigm shift in pharma R&D? *Drug Discov Today*. 2022;27:2395–2405. https://doi.org/10.1016/j.drudis.2022.05.018.
41. Chesbrough H. *Open Innovation: The New Imperative for Creating and Profiting, from Technology*. Boston: Harvard Business School Press; 2003.
42. Schuhmacher A, Germann PG, Trill H, Gassmann O. Models for open innovation in the pharmaceutical industry. *Drug Discov Today*. 2013;18:1133–1137. https://doi.org/10.1016/j.drudis.2013.07.013.
43. Rafols I, Hopkins MM, Hoekman J, Siepel J, O'Hare A. Big Pharma, little science? A bibliometric perspective on Big Pharma's R&D decline. *Technol Forecast Soc Change*. 2014;81:22–38. https://doi.org/10.1016/j.techfore.2012.06.007.
44. Ural A, Ramko R, Signhania A. How do biotechs stay the course in uncharted waters? Beyond borders: EY biotechnology report 2022. EY; 2022. https://assets.ey.com/content/dam/ey-sites/ey-com/en_us/topics/life-sciences/ey-beyond-borders-2022-report-v8-web-hires.pdf. Accessed January 1, 2023.
45. Smietana K, Quigley D, Van de Vyver B, Møller M. The fragmentation of biopharmaceutical innovation. *Nat Rev Drug Discov*. 2020;19:17–18. https://doi.org/10.1038/d41573-019-00046-3.
46. Weng C, Rogers JR. AI uses patient data to optimize selection of eligibility criteria for clinical trials. *Nature*. 2021;592:512–513. https://doi.org/10.1038/d41586-021-00845-y.
47. Li Y et al. Discovery of potent, selective, and orally bioavailable small-molecule inhibitors of CDK8 for the treatment of cancer. *J Med Chem*. 2023;66:5439–5452. https://doi.org/10.1021/acs.jmedchem.2c01718.
48. Walters WP, Murcko M. Assessing the impact of generative AI on medicinal chemistry. *Nat Biotechnol*. 2020;38:143–145. https://doi.org/10.1038/s41587-020-0418-2.
49. Zhavoronkov A et al. Deep learning enables rapid identification of potent DDR1 kinase inhibitors. *Nat Biotechnol*. 2019;37:1038–1040. https://doi.org/10.1038/s41587-019-0224-x.
50. Savage N. Drug discovery companies are customizing ChatGPT: here's how. *Nat Biotechnol*. 2023;41:585–586. https://doi.org/10.1038/s41587-023-01788-7.
51. A. Zhavoronkov, From target discovery to phase 1 initiation in under 30 months: AI discovered and designed drug enters the clinic, *Nature* https://www.nature.com/articles/d43747-022-00112-7. Accessed January 1, 2023.
52. Teece D, Pisano G. Dynamic capabilities of firms. In: Holsapple CW, editor. *Handbook on knowledge management*, vol. 2. INFOSYS; 2003:195–213.
53. Teece DJ, Pisano G, Shuen A. Dynamic capabilities and strategic management. *Strateg Manag J*. 1997;18:509–533. https://doi.org/10.1002/(SICI)1097-0266(199708)18:7<509::AID-SMJ882>3.0.CO;2-Z.
54. Jayatunga MKP, Xie W, Ruder L, Schulze U, Meier C. AI in small-molecule drug discovery: a coming wave? *Nat Rev Drug Discov*. 2022;21:175–176. https://doi.org/10.1038/d41573-022-00025-1.
55. Nagra NS, Joachim Bleys, Champagne D, Devereson A, Macak M. Understanding the company landscape in AI-driven biopharma R&D. https://doi.org/10.1038/d43747-023-00020-4.
56. Schuhmacher A, Haefner N, Honsberg K, Goldhahn J, Gassmann O. The dominant logic of Big Tech in healthcare and pharma. *Drug Discov Today*. 2023;28. https://doi.org/10.1016/j.drudis.2022.103457 103457.
57. Cohen WM, Levinthal DA. Absorptive capacity: a new perspective on learning and innovation. *Adm Sci Q*. 1990;35:128–152. https://doi.org/10.2307/2393553.
58. Bourla A. The CEO of Pfizer on developing a vaccine in record time. Harvard Business Review; 2020. https://hbr.org/2021/05/the-ceo-of-pfizer-on-developing-a-vaccine-in-record-time. Accessed May 18, 2022.
59. Lindborg SR, Persinger CC, Sashegyi A, Mallinckrodt SJ, Ruberg SJ. Statistical refocusing in the design of Phase II trials offers promise of increased R&D productivity. *Nat Rev Drug Discov*. 2014;13:638–640. https://doi.org/10.1038/nrd3681-c1.
60. Cha M, Rifai B, Sarraf P. Pharmaceutical forecasting: throwing darts? *Nat Rev Drug Discov*. 2013;12:737–738. https://doi.org/10.1038/nrd4127.
61. Schulze U, Ringel M. What matters most in commercial success: first-in-class or best-in-class? *Nat Rev Drug Discov*. 2013;12:419–420. https://doi.org/10.1038/nrd4035.

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