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Profitability and drug discovery

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Abstract

Pharmaceutical firms are highly profitable due to high markups enabled by high drug prices. This is justified by the argument that high profits provide incentives for innovation and help fund high research and development (R&D) costs. We investigate the link between past profitability and drug discovery for large publicly-listed pharmaceutical firms between 1980 and 2018. Our sample includes 118 firms with 2534 firm-year observations and in terms of sales corresponds to 55% of the global spending on drugs. By merging three data sets on firm financials, new patent applications, and new drug approvals, we show that pharmaceutical firms' markups and profitability are consistently higher than average nonfinancial firm profitability, with secularly increasing trends since 1980. Whereas R&D spending has also increased, the number of new drug approvals has not increased at the same pace and the productivity of R&D spending has been declining. In statistical analysis, we fail to identify any strong positive relationship between profitability and new drug discovery. Results are broadly in line with the earlier findings of research on the pharmaceutical industry and provide a contribution to the discussion on the link between profitability and innovation as well as on formulating policies for increasing drug innovation and ensuring the provision of essential drugs while keeping their costs low.

JEL classification: E22, I11, L25, L65

1. Introduction

The Covid-19 pandemic once again put the pharmaceutical industry under the spotlight. While developing a number of vaccines in a historically short time span was recognized as an extraordinary achievement and the perception about pharmaceutical firms turned "from greedy patent exploiters to the saviors of humankind,"[1] some were quick to point out the essential role of public funds and technology behind this success[2] and how monopolization of the vaccine production through patents decreases the overall social welfare of the world population.[3] In fact, profitability, productivity, and innovation capacity of the pharmaceutical industry have long been subject to detailed investigations and controversy. The recent body of research suggests that it has consistently been among the most profitable industries (Spitz and Wickham, 2012; Ledley *et al.*, 2020), while, at the same time, it is one of the most research-intensive industries measured by research and development (R&D) spending and the number of patents (Rikap, 2021: 99). However, despite high profitability and high R&D spending, a productivity crisis has been affecting the industry as indicated by a decline in pharmaceutical innovation (e.g., Munos, 2009; Paul *et al.*,

1 Forget the "beginning of the end", Covid is a permawar, *Financial Times*, Retrieved May 7, 2021 from https://www.ft.com/content/1c7266b1-1fad-458e-8585-12dc3164fdce.
2 Governments must demand all coronavirus COVID-19 vaccine deals are made public, *MSF*, Retrieved May 7, 2021 from https://www.msf.org/governments-must-demand-all-coronavirus-covid-19-vaccine-deals-are-made-public.
3 Want Vaccines Fast? Suspend Intellectual Property Rights, *The New York Times*, Retrieved May 7, 2021 from https://www.nytimes.com/2020/12/07/opinion/covid-vaccines-patents.html.

2010; Pammolli *et al.*, 2011; Khanna, 2012; Scannell *et al.*, 2012; Scannell and Bosley, 2016), which, according to some, is due to the increased financialization and shareholder value focus of the industry (Montalban and Sakınç, 2013; Lazonick *et al.*, 2017; Tulum and Lazonick, 2018). The high cost of drugs in the USA has also led to a criticism of the high markups of the industry (Kesselheim *et al.*, 2016), while others defended the high profits on two grounds: it gives incentives for innovation and helps pharmaceutical firms recoup high R&D costs to continue investment in R&D and innovation (e.g., DiMasi *et al.*, 2003, 2016). Yet, these grounds have also been challenged as it has been argued that most of the new drugs that come to the market are not invented by the large and highly profitable pharmaceutical firms but by smaller labs and through partnerships with publicly funded research labs (Jung *et al.*, 2019; Rikap, 2021).

We focus on the profitability and productivity of large pharmaceutical firms by combining and analyzing three different data sets on firm financial statements, patents, and new drugs approved by the Food and Drug Administration (FDA). We specifically focus on the link between profitability and innovation as measured by new drug approvals. Our analyses reveal four things: First, large pharmaceutical firms indeed charge higher markups and earn higher profits compared with the average markups and profitability of the rest of the nonfinancial corporate sector; and both rates have significantly increased over time. Second, while it is true that they devote a higher share of their profits to R&D, this share has declined in the late 2000s and only recovered to its previous high after the mid-2010s, whereas payments to shareholders have been taking up a much larger share of pharmaceutical firms' profits. Third, even though the total number of patents filed by the pharmaceutical firms has significantly increased, new drug or biologics license approvals, especially ones constituting highly innovative forms have slowed down and R&D productivity measured in terms of drug innovation has been declining. Fourth, firm-level statistical analyses show no evidence of a positive relationship between profitability and drug innovation. These results are broadly in line with the earlier findings of research on the pharmaceutical industry and provide a contribution to the discussion on the link between profitability and innovation as well as on formulating policies for increasing drug innovation, ensuring the provision of essential drugs, while keeping their costs low.

2. Profitability and innovation

The pharmaceutical industry is perhaps one of the most researched industries. There is a voluminous literature in economics, business, and finance investigating various dynamics of the industry. While we will not attempt to present yet another review of this literature (for a recent review of the literature, see Lakdawalla, 2018), it is important to highlight that a central question regarding the industry has been the link between its high profitability and innovation capacity. This is because the pharmaceutical firms are among the most profitable in the nonfinancial corporate sector and their business model essentially depends on continuous innovation. A number of recent studies compare the profitability of large pharmaceutical firms with the rest of the nonfinancial corporate sector and find that pharmaceutical firms' profitability has been significantly higher than average profitability (e.g., Spitz and Wickham, 2012; Ledley *et al.*, 2020). This high profitability has been accompanied by high R&D spending and a large number of patents produced (Rikap, 2021: 99). The high markups and profitability of the industry drew criticism, especially because of the high costs of drugs in the USA (Kesselheim *et al.*, 2016).

It has generally been argued that the monopoly rents arising from patent protections and the resultant high profits are necessary rewards for high risk-taking. Innovations that provide monopoly rents and high profits will generate larger funds to further invest in R&D and for further innovation. These arguments are reminiscent of Schumpeter's (1942) two types of innovative regimes. The first one, Mark 1, is the entrepreneurial regime that is mostly dominated by small innovative firms; and the second one, Mark 2, is the regime where innovations are mostly carried out by large established firms While the former is referred to as "creative destruction", the latter is referred to as "creative accumulation." In the latter, the R&D efforts of the large firms are sustained by the high profits of the previous periods that help finance innovative activities. Along these lines, Nordhaus (1969) argues that investments in innovation increase with high expected profits from innovation. Hence, the high profitability of the pharmaceutical firms is defended.

First, on the ground that the monopoly rents that are behind the high profits generate incentives for taking risks and innovating. Second, since not all R&D activity results in profitable innovation, high profits are also seen as necessary for recouping these high R&D costs (e.g., DiMasi *et al.*, 2003, 2016).

There has been a number of empirical studies looking at profitability, cash flow, and R&D relationship for pharmaceutical firms. For example, Scherer (2001) finds that short-term deviations in profitability predict R&D expenditures, while works such as Grabowski (1968) and Grabowski and Vernon (2000) find that cash flow is an important determinant of R&D expenditures. However, as Lakdawalla (2018: 415) also notes most of this literature has not been clear whether the explanation relies on a financial constraints argument or a profitability argument. Yet, a number of recent studies point out that the industry has been suffering from a productivity crisis as revealed by the decline in pharmaceutical innovation (e.g., Munos, 2009; Paul *et al.*, 2010; Pammolli *et al.*, 2011; Khanna, 2012; Scannell *et al.*, 2012; Scannell and Bosley, 2016). Focusing on this productivity crisis, Montalban and Sakınç (2013), for example, emphasize that the business model of the pharmaceutical industry in the USA has historically been based on "the exploitation of monopoly rents of innovation" and was supported by large amounts of public funding of basic research and strong patent protections. (p. 992). They go on to argue that a large part of this productivity crisis is due to increased financialization and shareholder value focus of the industry (Montalban and Sakınç, 2013; Lazonick *et al.*, 2017; Tulum and Lazonick, 2018). In fact, some recent works argue that the existing innovation models of the pharmaceutical industry not only lack directionality to meet key needs but also lead to inefficient collaboration (Mazzucato and Li (2021: 39).

Another significant challenge to the argument about profitability and innovation is that most of the new drug innovation does not come from highly profitable, large pharmaceutical firms but from smaller labs and/or publicly funded research labs (Jung *et al.*, 2019; Rikap, 2021). In fact, according to this argument, large pharmaceutical firms profit from the marketing of the innovations that are due to small labs and/or publicly funded research labs.

In the light of these discussions on the link between profitability and innovation, we ask in the following sections whether it is possible to empirically identify a link between profitability of the large pharmaceutical firms and their drug innovation.

3. Data and sample

We start by merging three data sets. Firm-level financial data come from Standard and Poor's *Compustat* database, which includes all publicly-traded firms on North American stock exchanges. The Standard Industry Classification (SIC) code 2834 captures the pharmaceutical preparation firms in the database. The majority of the leading drug producers such as Novartis, Pfizer, Merck & Co, and Abbott Laboratories are classified under this code. However, closer examination reveals that SIC codes 2835 (In Vitro and In Vivo Diagnostic Substances) and 2836 (Biological Products, Except Diagnostic Substances) also include major new drug producers such as Gilead Sciences, Amgen, and Lexicon Pharmaceuticals. Therefore, we start by including all firms classified under these three codes in our sample. Second, using the unique firm identifier (gvkey) we merge these data with the *PatentsView* patent data, which includes patents granted by the US Patent and Trademark Office, by using Kogan *et al.* (2017) and Global Corporate Patent Dataset of Bena *et al.* (2017). Third, we merge the FDA@Drug data set, which includes information on FDA-approved drug applications with the financial and patent data by manually matching drug sponsor names with the Compustat company names and firm identifiers (gvkey).

From this merged data set, we form our sample by dropping firms that have no new drugs between 1980 and 2018 and then keeping firms that were among the top 50 firms by total sales at least 1 year in the same period. This final sample enables us to focus on evaluating the industry's long-run drug discovery performance and to alleviate a potential problem of the composition effect that may result from the inclusion of the firms that entered into and exited from the sample

Table 1. Variable definitions

	Definitions	Compustat/FDA item name
Profit rate	(Operating income before depreciation—income taxes)/Property, plant, and equipment	(oibdp—txt)/ppent
Return on assets	Net income/Total assets	ni/at
Return on equity	Net income/Total equity	ni/seq
Markup rate	(Sales—cost of goods sold)/Sales	(sale—cogs)/cogs)
Indebtedness	(Long-term total debt + debt in current liabilities)/Total assets	(dltt + dlc)/ at
Tobin's *Q*	(Market value + Liabilities + Preferred stock)/ Total assets	(prcc_f * csho)+ lt + pstk)/at
R&D to cash flow ratio	R&D/Cash flows	xrd/(oibdp—txt)
Shareholder payments to cash flow ratio	(Purchase of common and preferred stock + Cash dividends) /Cash flows	(prstkc + dv)/(oibdp—txt)
ND1	A prescription or over-the-counter drug/biological product that contains a new molecular entity (Type 1), new active ingredient (Type 2), new dosage form (Type 3), new combination (Type 4), new formulation or new indication and claim (Type 5) and the other type of combinations (Type 1/4, Type 2/3, Type 2/4, Type 3/4, Type 4/5).	
ND2	A prescription or over-the-counter drug/biological product that contains a new molecular entity (Type 1) or new active ingredient (Type 2).	

for a short time interval.[4] Our final sample includes income and balance sheet data, new patent application data, and new drug approval data for 118 firms with 2534 firm-year observations. This sample recorded a total sale of $668 billion in 2018, corresponding to around 55% of the global spending on medicines in that year (IQVIA, 2019).

FDA defines a new drug as a prescription or over-the-counter drug/biological product that contains a new molecular entity (Type 1), new active ingredient (Type 2), new dosage form (Type 3), new combination (Type 4), new formulation or new indication and claim (Type 5), and the other type of combinations (Type 1/4, Type 2/3, Type 2/4, Type 3/4, and Type 4/5) in addition to previously marketed products without an approval (Types 7, 8), or products that are duplicate of a drug that has a pending or approved new drug/biologics license application (Type 10).[5] However, there is growing concern that pharmaceutical firms introduce "me-too" drugs in these secondary forms in order to extend the patent and exclusivity period to avoid generic competition (Wieseler *et al.*, 2019; Rajkumar, 2020). In his detailed discussion of claims relating to pharmaceutical innovations, Correa (2007) suggests that new formulations and compositions as well as processes for their preparation, combinations of known active ingredients, new doses of known products should be deemed obvious in the light of prior art. We follow him in defining the new drug variables. Our first and broader definition, **ND1**, includes all new drug approvals (NDAs) and biologics license approvals (BLAs) classified under Types 1, 2, 3, 4, 5, 1/4, 2/3, 2/4, 3/4, and 4/5. Our second and narrower definition, **ND2**, includes only a prescription or over-the-counter drug/biological product (i.e., both NDAs and BLAs) that contains a new molecular entity (Type 1) or new active ingredient (Type 2).

It should be kept in mind that a firm can still get a new drug approval even if the active ingredient of the drug has been approved for other indications within a certain time frame. Also, a Type 1 or Type 2 drug lacking much therapeutic value may also be approved as long as FDA

4 In the firm-level statistical analysis below, we use different samples based on different and more balanced subsamples to check whether our main results are robust to such a potential composition effect.

5 See Table 1 for a more detailed discussion of the definitions. A drug being reviewed under different submission classification code is classified under Type 9, when the applicant has no intention to market the product under Type 9 NDA after FDA approval. Type 6 is no longer used by the FDA and it is replaced with Type 9 and Type 10.

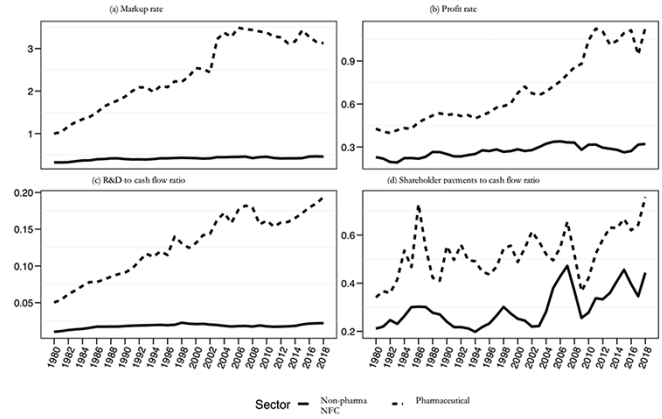

Figure 1. Profitability and its uses.
Notes: The Compustat pharmaceutical sample that has at least one drug and was among the top 50 firms by total sales at least 1 year between 1980 and 2018 and the non-pharma NFC sample that includes the nonfinancial corporations other than pharmaceutical firms and that excludes the utilities. Excluded financial corporations are classified under SIC codes 6000–6800 and utilities are classified under SIC codes 4900–4999. Markup rate is (Sales—Cost of Goods Sold)/Sales; profit rate is defined as (Operating Income Before Depreciation—Income Taxes)/Property, Plant and Equipment; Shareholder payments is defined as (Purchase of Common and Preferred Stock + Cash Dividends) /(Operating Income Before Depreciation—Income Taxes); finally, R&D expenditures is captured by R&D /(Operating Income Before Depreciation—Income Taxes). For the Compustat item names of the financial variables used, see variable definitions.

requirements are met. In either case, we would be overestimating the number of new drugs even with the narrower ND2 definition and our findings below would still be valid.[6]

4. Profitability and drug discovery: industry trends

4.1 Profitability and its uses

We summarize the trends in markups, profit rates, R&D-spending-to-cash-flow ratio, and shareholder-payments-to-cash-flow ratio for our sample in comparison with the rest of the nonfinancial firms in the Compustat database in Figure 1. The markup rate increases secularly from the early 1980s to the mid-2000s and remains quite high, even though there seems to be a declining trend after its peak. Similarly, the profitability of pharmaceutical firms consistently increases from the early 1980s to the early 2010s. While there are two declines followed by quick recoveries in profitability in the 2010s, the rate remains historically high. Both the markups and the profitability of the pharmaceutical firms are significantly higher than the rest of the nonfinancial corporate sector.

The lower part of Figure 1 shows the two main uses of these profits: R&D investments and shareholder payments. While the pharmaceutical industry has been increasing its R&D spending throughout the 1980s and the 1990s, there is a slowdown in the 2000s, which is only reversed by the early 2010s. It is possible that the slowdown in the growth of R&D spending was the result of mega mergers that took place in the late 1990s and the early 2000s, which were often followed by major restructuring of R&D operations. For example, LaMattina (2011), former President of Pfizer Global Research and Development, notes that major mergers in the pharmaceutical industry had resulted not only in cuts to the R&D operations but also the elimination of entire research sites in some cases. Similarly, the increase in the following period could be the result of the acquisition spree that the large pharmaceutical firms had engaged in this period.[7] Furthermore, in Figure 1(d), we observe that the pharmaceutical firms consistently devoted a

6 We thank an anonymous referee for pointing this out.
7 We would like to thank the anonymous referees for pointing out these two possibilities.

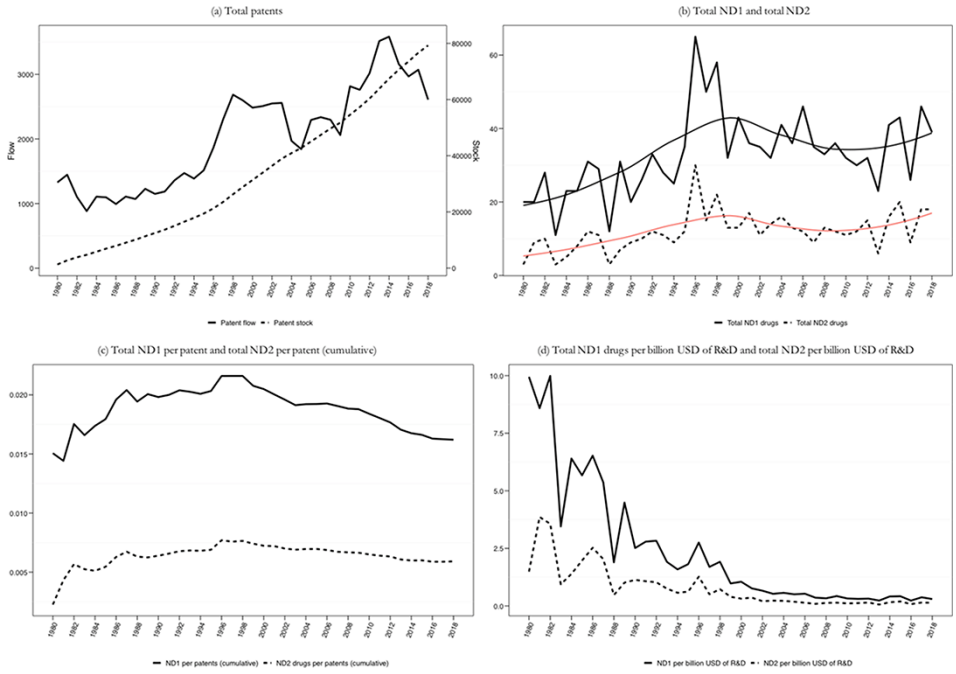

Figure 2. Patents, drug discovery, and R&D productivity.
Notes: The Compustat pharmaceutical sample that has least one drug and was among the top 50 firms by total sales at least 1 year between 1980 and 2018. ND1 is the number of new prescription or over-the-counter drug/biological product that contains a new molecular entity (Type 1), new active ingredient (Type 2), new dosage form (Type 3), new combination (Type 4), new formulation or new indication and claim (Type 5) and the other type of combinations (Type 1/4, Type 2/3, Type 2/4, Type 3/4, and Type 4/5). ND2 is the number of new prescription or over-the-counter drug/biological product that contains a new molecular entity (Type 1) or new active ingredient (Type 2). In panel (b), smoothed lines show the unconditional means, aiding in seeing the regularities in the drug discovery.

larger share of their profits to shareholder payments than to R&D investment. While the trend in shareholder payments of the pharmaceutical industry follow the general trend of the rest of the nonfinancial corporate sector, the levels are consistently higher.

4.2 Patents, drug discovery, and R&D productivity

The high profitability of the pharmaceutical industry is defended on two grounds: First, prospects of high profitability provide an incentive for innovation and drug discovery as developing drugs is a high-risk and low-probability process. Second, developing drugs is costly and firms need to recoup the high R&D costs of both successful and unsuccessful attempts. In Figure 2, we turn to the innovation side. Panel (a) shows that the number of total patents of the sample has been increasing. There are two periods of acceleration in new patent applications, one in the early 1990s and then in the late 2000s into the early 2010s. However, new drug discovery, shown on panel (b), seems to follow a more stagnant path since the early 2000s, both for ND1 and ND2. Clearly, new drug discovery shows a more volatile pattern but the upward trend of the 1980s and 1990s is reversed in the early 2000s. The increases in numbers in the 2010s so far appear not to have been persistent as they are followed by quick drops afterward.

When we look at the relationship between new drugs and total patents in panel (c), we observe that after its peak in the late 1990s, new-drugs-to-patents ratio has been declining. It is well known that a simple patent count is usually not indicative of much as there is great variation in the value and significance of patents. Panel (c) also shows that the increase in the number of patents does not correspond to an increase in drug innovation. While the common belief is that

patents are granted for new drugs, these statistics challenge that view and seem more in support of the view that a significant portion of the new patents essentially cover minor modifications of already existing drugs (Correa, 2007: viii). Furthermore, a patent is filed after the discovery of a new compound, but well before its clinical approval and use (Lakdawalla, 2018: 399). It is also possible that pharmaceutical firms are developing and patenting process innovations and not only new drugs. Dosi *et al.* (2021: 8) show that since the early 2000s patents that belong to process innovations have been somewhere between 20–35% of total patents, with considerably sharp variations from one year to the other.

Finally, while Figure 1(c) showed that the R&D spending of the firms as a ratio of their profits has been increasing, Figure 2(d) shows that the productivity of this R&D spending in terms of new drug discovery has been on the decline. This decline could be due either to the increasing difficulty of developing new drugs or to firms directing their R&D more towards modifications of existing drugs in order to protect their market dominance and profitability. While it is not possible to distinguish which cause dominates this trend, we turn to the implications of these possibilities in the conclusion.

In Table 2, we summarize all these variables by decade averages in order to get a broader view of the performance of the pharmaceutical industry. While average profitability has increased for all groups throughout decades, the increase in the share of profits devoted to R&D has increased only slowly and started declining in the 2010s. However, we observe that more of the profits has been used to make payments to the shareholders. Parallel to these trends despite a significant increase in the number of patents, the number of new drugs is declining. These results are in line with the argument that financialization has been detrimental to innovation as firms are allocating more of their income to shareholders instead of retaining earnings to support organizational innovation efforts.

The last three columns of Table 2 show the percentage changes in average profitability and new drug discovery. These columns also provide a cursory indication that large percentage increases in profitability do not correspond to similar increases in drug discovery. In fact, despite large increases in profitability, ND1 discovery shows a negative percentage change in the 2010s and ND2 discovery shows a negative percentage change in the 2000s. Similarly, sample scatterplots of past profitability and R&D expenses, ND1, and ND2 also provide cursory evidence of the absence of a link between profitability and either R&D or new drug discovery as we show in the next section.

5. Profitability and drug discovery: firm-level analysis

To motivate the empirical analysis in the following section, we look at the relationship between profitability, R&D, and drug discovery at firm-level in Figure 3. Panel (a) focuses on the association between the 5-year average profitability and the R&D expenditures in the next 5-year period for the firms in our sample. In the scatterplots, we choose 5-year average profitability instead of simply looking at the relationship between past year's profitability and this year's R&D and drug discovery since the drug innovation is a long process as we discuss more in detail in the next section. The scatterplots do not significantly change when we take shorter or longer periods of time.

We observe in panel (a) that firms with a low level of average R&D expenditures despite higher levels of average profitability in the past coexist with firms that invest more in R&D despite relatively low past profitability, showing that there is no clear relationship between past profitability and current R&D expenditures. In Panel (b), we observe that the firms with an average past profitability lower than 30% discovered, on average, less new drugs (ND1) in the following periods, while this relationship disappears after the 30% threshold. As panel (c) indicates, the same picture applies to more innovative forms of new drugs (ND2).

6. Regression analysis

Sample averages and firm-level analysis presented above constitute a largely descriptive overview of the absence of a relationship between profitability and drug discovery. In this section we test,

Table 2. Profitability, R&D, and new drug discovery—period or annual averages

	Profitability	R&D/CF	Shareholder pay/CF	Avg. number of patents	Avg. number of ND1s	Avg. number of ND2s	Avg. number of new drug per USD of R&D	Change in avg. profitability (%)	Change in avg. number of ND1s (%)	Change in avg. number of ND2s (%)
The top 50 firms by total sales at least 1 year between 1980 and 2018 with at least one new drug approval										
1980s	0.46	0.47	0.47	1136.4	22.8	7.1	0.38			
1990s	0.55	0.58	0.5	1752.7	37.2	14.3	0.12	19.57	63.16	101.41
2000s	0.75	0.64	0.53	2290	37.3	13	0.03	36.36	0.27	–9.09
2010s	1.07	0.58	0.61	3055.33	34.67	13.89	0.02	42.67	–7.05	6.85

Notes: The table shows the pharmaceutical industry's financial performance, ability to discover new drugs, and patenting activity by decades during the period of 1980–2018. The data come from the Compustat pharmaceutical sample that has at least one drug and was among the top 50 firms by total sales at least 1 year between 1980 and 2018. Profitability is defined as (Operating Income Before Depreciation—Income Taxes)/Property, Plant and Equipment; Shareholder payment is defined as (Purchase of Common and Preferred Stock + Cash Dividends) /Cash Flows; and R&D expenditures is captured by R&D/Profits. ND1 is the number of new prescription or over-the-counter drug/biological product that contains a new molecular entity (Type 1), new active ingredient (Type 2), new dosage form (Type 3), new combination (Type 4), new formulation or new indication and claim (Type 5) and the other type of combinations (Type 1/4, Type 2/3, Type 2/4, Type 3/4, Type 4/5). ND2 is the number of new prescription or over-the-counter drug/biological product that contains a new molecular entity (Type 1) or new active ingredient (Type 2). For the Compustat item names of the financial variables used, see variable definitions. The first panel focuses on the firms that has least one drug and was among the top 50 firms at least one year between 1980 and 2018, while the second panel excludes the non-US incorporated firms from the benchmark sample. Average number of patents is obtained through the PatentView data matched with the Compustat sample using assignee gvkey identifiers provided by Kogan *et al.*'s (2017) and Bena *et al.*'s (2017) Global Corporate Patent Dataset.

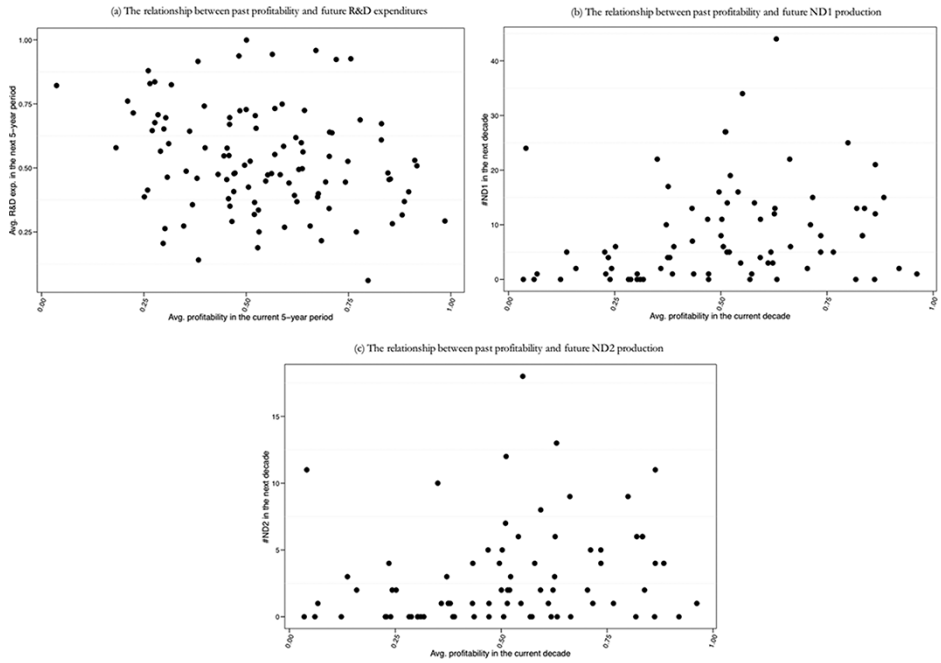

Figure 3. Past profitability and its relationship with R&D expenditures and drug discovery.
Notes: The Compustat pharmaceutical sample that has least one drug and was among the top 50 firms by total sales at least 1 year between 1980 and 2018. Outlier firms with excess negative/positive profitability and R&D expenditures are excluded. ND1 is the number of new prescription or over-the-counter drug/biological product that contains a new molecular entity (Type 1), new active ingredient (Type 2), new dosage form (Type 3), new combination (Type 4), new formulation or new indication and claim (Type 5) and the other type of combinations (Type 1/4, Type 2/3, Type 2/4, Type 3/4, Type 4/5). ND2 is the number of new prescription or over-the-counter drug/biological product that contains a new molecular entity (Type 1) or new active ingredient (Type 2). Profitability is defined as (Operating Income Before Depreciation—Income Taxes)/Property, Plant and Equipment; R&D expenditures is captured by R&D/Cash Flows. For the Compustat item names of the financial variables used, see variable definitions.

through regression analysis, whether it is possible to identify a positive relationship between profitability and drug discovery at the firm level, while controlling for other financial variables that potentially play an important role in drug discovery. Due to the peculiar R&D intensity of pharmaceutical investment, we treat R&D and drug innovation as investment decisions and regress commonly discussed determinants of investment expenditures in the economics literature as our explanatory variables in addition to profitability.

Profits are claimed to be the main incentive to sustain R&D efforts and to be internal financial resources in the absence of external funds available in the financial market due to high risk of drug innovation. Despite high profitability, however, firms still may be unwilling to invest in R&D and in drug innovation, if there exists a trade-off between expected future returns, capital stock, and the cost of investment. Tobin's Q partially quantifies this trade-off under the assumption that firms are able to form expectations of the future and that the objectives of the managers are in line with that of shareholders. A Tobin's Q greater than 1 then implies that returns from the investment are larger, when the market value of the firm exceeds the face value of its total assets. Therefore, we add Q as our first financial control variable.

In this framework, however, even a large Q and high profitability may not be enough for investment in R&D and new drug production, if firms are financially constrained by their debt structure. Internal resources may need to be used to pay long-term total debt and debt in current liabilities. Hence, we add firm indebtedness as our second control variable.

Finally, some years may be subject to extreme deviations in outcome variables and explanatory variables, while some firms in our sample may have time-invariant structural and organizational differences. Therefore, we also include firm- and year-specific fixed effects as control variables.

We estimate the following three equations in which profitability and control variables are regressed on R&D, ND1, and ND2 in turn (where α_i and δ_t therefore denote a full set of firm-specific effects and of year-specific effects, and ε_{it} is the error-term that captures the effects of time-variant unobservables on outcome variables):

$$\text{R\& D}_{it} = \text{profitablity}_{it-1} + \text{Tobin'sQ}_{it-1} + \text{Indebtedness}_{it-1} + \alpha_i + \delta_t \tag{1}$$

$$\begin{aligned}\text{ND1}_{it} = {} & \text{s year avg. profitablity}_{it-10} + \text{s year avg. Tobin'sQ}_{it-10} \\ & + \text{s - year avg. Indebtedness}_{it-10} + \alpha_i + \delta_t\end{aligned} \tag{2}$$

$$\begin{aligned}\text{ND2}_{it} = {} & \text{s year avg. profitablity}_{it-10} + \text{s year avg. Tobin'sQ}_{it-10} \\ & + \text{s year avg. Indebtedness}_{it-10} + \alpha_i + \delta_t\end{aligned} \tag{3}$$

We use the standard within estimator to estimate the parameters of the model. In other words, the parameters are obtained by regression of $y_{*it} = y_{it} - \overline{y_i} - \overline{y_t} + \overline{\overline{y}}$ on $x_{*it-j} = x_{it-j} - \overline{x_i} - \overline{x_{t-j}} + \overline{\overline{x}}$, where $\overline{y_i} = \frac{1}{T}\sum_{t}^{T} y_{it}$ is the firm mean, $\overline{y_t} = \frac{1}{n}\sum_{i=1}^{n} y_{it}$ is the year mean and $\overline{\overline{y}} = \frac{1}{nT}\sum_{i}^{n}\sum_{t}^{T} y_{it}$ is the overall mean of the outcome variables R&D, ND1, and ND2 likewise for explanatory variables *xs* including profitability, Tobin's *Q*, and indebtedness. Hence, a positive and large estimated coefficient for the profitability variable would show that the firms whose *s*-year average profitability in time *t-j* is greater than their own long-term profitability during the entire sample period and greater than profitability of the entire sample in time *t-j* perform better in terms of R&D expenditures and drug innovation in time *t*, holding constant the expected return and financial constraint.

The main concern here is the choice of *j*. In equation (1) the link between profitability, expected returns, and R&D expenditures can be conceived of as a short-term relationship. If the firm *i* in year *t-1* expects a higher return and has a profit margin as an internal resource free from the financial constraint, it will invest in R&D in *t*. By contrast, drug innovation is a long process. At the discovery stage, pharmaceutical firms create a new molecule or select an existing one, test its efficiency, and select one or more successful drug candidates. The safety of the candidate drug is tested using animal and lab models. A further stage involves initial submission, clinical trials, and new drug application. The approval follows the clinical development stage, if the drug is proved to be safe for patients to use. This entire drug development cycle may last at least 10 years *on average* (PhRMA, 2015). Hence, in equations (2) and (3) what matters for drug innovation may not be profitability in time *t-10* but profitability in time *t-11* or in time *t-14* etc. Our data do not allow us to capture the between-drug variation in R&D time. However, it is reasonable to expect that firms whose past *s*-year average of profitability in time *t-j* is high relative to its own average and to sample average have more incentive and internal finance to manufacture a new drug approved by FDA in time *t*. In our benchmark specification we proceed by examining if past 5-year average of profitability in *t-10* is associated with drug innovation in time *t*. But we allow both *j* and *s* to vary across alternative specifications as discussed below under robustness.

Table 3 reports the results from our specification. Notice that for all coefficients' sampling errors are too large for the statistical inference to be conclusive—in other words, we fail to find any statistically significant relationship between the dependent and independent variables. With this caution in mind, we look at the relationship between R&D expenditures in the current year and profitability in the preceding year in column 1. We find an economically insignificant coefficient, implying that higher profitability is not necessarily associated with higher R&D

Table 3. Effects of profitability on R&D and drug discovery

		Dependent variables	
	R&D	Number of ND1s	Number of ND2s
	(1)	(2)	(3)
Profitabilityt – 1	0.008		
	(0.027)		
T obin0 sQt – 1	0.008		
	(0.582)		
Indebtednesst – 1	–8.375		
	(7.201)		
Average past 5 year profitability in t – 10		0.003	–0.0002
		(0.002)	(0.001)
Average past 5 year Tobin's Q in t – 10		0.001	0.003
		(0.013)	(0.007)
Average past 5 year in Indebtedness t – 10		–0.172	–0.034
		(0.135)	(0.073)
Observations	1755	1751	1751
R2	0.065	0.439	0.281
Residual Std. Error	56.501 (df = 1618)	0.921 (df = 1614)	0.497 (df = 1614)
F Statistic	0.821 (df = 136; 1618)	9.285 (df = 136; 1614)	4.630 (df = 136; 1614)

Notes: The Compustat pharmaceutical sample that has at least one drug and was among the top 50 firms at least one year between 1980 and 2018. Firms with missing variables are dropped. Standard errors are shown in parenthesis. Profitability is defined as (Operating Income Before Depreciation—Income Taxes)/Property, Plant and Equipment; R&D expenditures is as the share of Cash Flows. Tobin's Q is (Market value + Liabilities + Preferred Stock)/ Total Assets. Indebtedness shows the (Long Term Total Debt + Debt in Current Liabilities)/Total Assets). . ND1 is the number of new prescription or over-the-counter drug/biological product that contains a new molecular entity (Type 1), new active ingredient (Type 2), new dosage form (Type 3), new combination (Type 4), new formulation or new indication and claim (Type 5) and the other type of combinations (Type 1/4, Type 2/3, Type 2/4, Type 3/4, Type 4/5). ND2 is the number of new prescription or over-the-counter drug/biological product that contains a new molecular entity (Type 1) or new active ingredient (Type 2). For the Compustat item names of the financial variables used, see variable definitions. For the Compustat item names of the financial variables used, see variable definitions.

investment. Similarly, Tobin's *Q* has a positive sign, but it is very small and imprecise. Hence, a higher expected return in the previous year does not predict a larger investment in R&D in the following year. Meanwhile, the indebtedness coefficient is negative and economically large. Firms constrained by their long-term debt in the previous year seem to invest less in R&D in the following year.

In columns 2 and 3, we focus on the number of new drug approvals. The profitability coefficient is close to zero, but positive for ND1 and nearly zero for ND2. All in all, looking at the economically very small but positive effect of profitability on the number of ND1s together with no effect of profitability on ND2 regression analyses provide no evidence of a statistically and economically significant impact of past profitability on R&D expenditures and drug innovation.

6.1 Robustness

A potential issue with the results presented above is that they may be vulnerable to the use of different definitions of profitability and R&D expenditures. Motivated by this, we use other measures of profitability such as return on assets and return on equity as key variables of interest and include R&D expenditures as a share of sales rather than profits. These estimates are presented in the Appendix. In Table S1 we show that our benchmark results are robust to the definition of outcome variables and explanatory variables. Return on equity is negatively correlated with R&D expenditures as a share of sales, the number of ND1, and the number of ND2. Return on asset, on the other hand, is in positive relationship with R&D but in negative relationship with drug innovation measures.

Although we limit our attention to the pharmaceutical firms that have at least one drug and were among the top 50 firms by total sales at least one year between 1980 and 2018, the Compustat sample may still be affected by the composition of initial public offerings. In other words, the fact that the number of relatively small public firms with only one drug that exit from the sample in a short period increases over time may lead to biased estimates. To avoid such a composition effect and unbalanced panel problem, we also construct a balanced panel focusing on the firms with at least 10 or 20 observations. In Table S2 we show that results are similar to our benchmark results. Finally, in Table S3, we examine the relationship between the number of new drugs and the profitability using different lags and moving average periods. Again, the results are nearly the same as presented in Table 3.

In short, the failure to establish an economically significant positive relationship between profitability and new drug discovery is robust to different variable definitions, different time lags as well as different subsample selections.

7. Concluding remarks

Neither descriptive statistics nor firm-level regression analyses support the view that high profitability leads to higher R&D spending and more drug discovery. The decline in pharmaceutical productivity despite consistently strong and high profitability is all the more worrying given that the intellectual property protections in place are now far stronger and the continuous increase in the number of patent applications show that the firms are taking full advantage of these protections. Clearly there are limits to the extent to which analyses based on patent or drug approval figures represent productivity. Factors such as the complexity of science involved in the disease areas companies focus, product novelty, the extent of the learning firms engage are all important to assess in determining the productivity of R&D and the sustainability of industrial growth. However, the decline in the number of new drug approvals as a ratio of new patent applications also show that looking at the patent applications may not be a good measure of R&D productivity and may be in more support of the view that firms use "patents of dubious validity" in order to protect their market power and deter entry into those markets (Baker, 2016: 35). Furthermore, as Mazzucato and Li (2021) note, the patent system may be preventing effective collaboration, which is vital for developing innovative solutions to complex problems since patenting is not only too wide and strong but also process patenting may be "blocking the ability of new, basic science to be fully disseminated, diffused, and translated into future innovation" (p. 41).

Diminishing returns in knowledge production and research being focused on increasingly more difficult targets are suggested as potential explanations for the decline in the R&D productivity of the pharmaceutical firms (Munos, 2009; Pammolli *et al.*, 2011). Then the question is, given increasing profitability, why do firms not respond to this by allocating a larger share of their profits to R&D expenditures? After all, high profitability of the pharmaceutical firms is often justified by their need for high R&D expenditures. Yet, we observe that firms prefer to devote a higher portion of their profits to shareholder payments rather than R&D expenditures. There are many warnings that the imperative of increasing profits and distributing them to shareholders could be pushing the firms to devote more sources to drugs that are deemed more profitable instead of drugs for diseases that are far more serious, especially for the lower income countries, while at the same time strong patent protections may be acting as an obstacle and deterrent for drug discovery in these countries.

The issue becomes more complicated as large pharmaceutical firms often do not develop new drugs themselves but acquire them from small labs (Jung *et al.*, 2019). Some have argued that the large firms acquired up to 70% of their revenues from products that were not developed by themselves.[8] In fact, by comparing the scientific co-publication and patent co-ownership of Roche, Pfizer and Novartis, Rikap (2019) identifies "a subordination of the universities, public research organizations and start-ups that have a fundamental role in the former, but an almost

8 Invent it, swap it or buy it, *The Economist*, Retrieved May 7, 2021 from https://www.economist.com/business/2014/11/15/invent-it-swap-it-or-buy-it.

negligible participation in the latter" (pp. 1006–7). If this is the case, then our analyses above may be overestimating the new drugs and hence the link between profitability and new drugs may actually be even weaker. Then the absence of a strong link between profitability and drug discovery also suggests that the large pharmaceutical firms may be highly profitable not because of their innovative capabilities but due to their monopolistic positions and marketing success. Large pharmaceutical firms may mostly be acquiring, developing and marketing drug innovations done elsewhere. This is in line with the argument that in contrast to the fundamental R&D carried out by actors at the bottom of the value chain, the pharmaceutical corporations' internal R&D mainly covers clinical testing and regulatory approval (e.g., Baranes 2016: 201).

Moreover, as the pharmaceutical industry expert Khanna (2012) shows the relationship between firms and public and academic research institutions have changed over time. Rikap (2021) finds that, based on publications' funding sources, top pharma firms outsource stage of their innovation networks to subordinate institutions and public agencies (universities and their hospitals, small R&D laboratories and public agencies) are main supporters of pharma research (p. 105). The Covid-19 vaccine race has also showed the significance of public support and funds.

All in all, these findings and arguments of the literature are in line with the absence of a significant empirical link between profitability and new drug discovery that we have presented in this paper.

Supplementary data

Supplementary materials are available at *Industrial and Corporate Change* online.

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Conflict of interest

Authors declare no competing interests.

Data availability

The financial data used in the paper come from the restricted-use Compustat database. Other data, code, and materials used in the analysis are available to any researcher for purposes of reproducing or extending the analysis.

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